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ANNALS OF INTERNAL MEDICINE

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NUMBER 1

PRESIDENTIAL ADDRESS

By ROGER I LEE, M D , F A C P , *Boston, Massachusetts*

THIS Annual Session of the American College of Physicians, this Convocation is a significant demonstration of the determining philosophy upon which the College is founded. Others may speak of the education and training in the professions of religion, teaching, engineering, the law, business, etc., but in the profession of medicine, and particularly in the medical specialties of which our College is a noteworthy illustration, it seems desirable to discuss from time to time certain outstanding features. As a preface to this discussion one may recall the emphasis that the late Charles W. Eliot, then President of Harvard University, put upon what he called the "prodigious advances in Medicine." That phrase is as true today as it was 35 years ago, and if one reads the times correctly, it will be even more true in another 35 years. Some of the oldsters among us look back on our student and hospital days in which there were no gastrointestinal roentgen-rays, no blood pressure apparatus, no determinations of the basal metabolic rate, no electrocardiograph, no Wassermann test, no cunning dyes that helped our diagnostic pursuit, no intravenous therapy, and very little of what we now call Chemotherapy. I mention only a few of a staggering list. And what of those from our ranks who tried to practice medicine with the education and training that they received only from the Medical School even when supplemented by a hospital internship¹. In charity we draw a veil over the direful possibilities.

It is axiomatic that the four years immediately after graduation from Medical School are more important than the four years in the Medical School. And this is true despite the inestimable value of the fundamental education in the Medical School. Moreover, this is a continuing process throughout a man's active medical life. The oldsters in their daily routine, in active practice at the bedside, in the clinic, in the laboratory and in teaching use techniques in diagnosis, treatment and in investigation that were unheard of in

* Address at the Annual Convocation of the American College of Physicians, St. Paul, Minnesota, April 22, 1942.

their student days Side by side the oldsters and the youngsters learn together The pace is "hot" The oldsters pant and sweat with the necessary exertion of learning the intricacies of the electrocardiograph or the electroencephalograph, for example, and of trying to understand the complexities and the inevitable jargon of immunology and of hormones, vitamins, and the like But to stop is to be lost It may be pride that drives us on, but I like to think that it is the excitement of the chase and the love of our profession And I like to think that therein lies the enduring satisfaction of our professional lives It is a satisfaction to recall that though inconspicuous and perhaps unsung and unquoted one took part in some of the prodigious advances in Medicine As I have said before, that is and must be the fundamental philosophy upon which the American College of Physicians stands

To those of you who are about to be received into Fellowship of the College, the College certifies that you have made notable progress in the Specialty of Internal Medicine You know and the College knows that your progress has not always been easy But mark you this, the College certifies only to your progress, not to your arrival at your professional destination Only physical or professional death will mark the end of your progress The excitement of these prodigious advances will, I fondly trust, continue to spur on your footsteps These next years, I assure you, will be even more vital to your progress than the years that have gone before The College hopes that this recognition of your progress in internal medicine will be accepted by you as evidence of your promise for the future Your futures will be even more varied than your pasts Some of you have already joined the armed forces of this country Perhaps most of you will eventually join the Army or Navy The rest of you will do double or makeshift duty in civilian practice, in the hospital, in teaching, or in the laboratory This tremendous dislocation of your professional lives is your bit and is to be accepted as your job For winning the war is at this moment the first and only job of every man, woman and child of this country, of every Fellow of this College and of the College itself

There are, however, real possibilities of prodigious advances in Army and Navy medicine, even though there are restrictions imposed by military necessities Some of you have already surmounted difficulties of a similar nature Some of you undoubtedly have labored under the restrictions imposed by such circumstances as locality, finances, inadequate equipment, unfavorable surroundings It is particularly to the credit of those when they have not only kept abreast of the rapid advances in medicine but also have kept their medical curiosity alert, so that on occasion they have pushed the frontiers forward

If the slogan of successful modern warfare is the offensive, always the offensive, the slogan of successful modern medicine, and indeed of this College might be the advance, always the advance, in the armed forces and in peace We must keep our enemies of disease and ignorance always on the defensive by never being on the defensive but always attacking, by readily

shifting plans to meet new situations. Disease and germs, like the Japs and Germans, always seek the initiative and always wage totalitarian war.

I realize that I have given a bald outline of one aspect of the ideology of this College. The College has tried to substantiate this ideology. The College recognizes its obligations to its Fellows and its country in peace and war. The College does not content itself with its Annual Meeting and the publication of the *ANNALS OF INTERNAL MEDICINE*, important and indeed vital as these two undertakings are. All of us need help in keeping up the pace of medical progress, and this is even more true in war than in peace. I speak advisedly when I say that the College has not yet met this obligation adequately, but important beginnings have been made. In the winter and spring of 1941, under the auspices and supervision of the College, seven postgraduate courses in internal medicine and related subjects were conducted for members of the College and other qualified physicians in medical centers all over the country. During the winter and spring of 1942 a somewhat more extended postgraduate course program was planned. Eleven courses were scheduled at widely separated medical centers, but due to war conditions five of them had to be withdrawn. The Annual Session of the College is actually a postgraduate week with its diversified program of clinics, panels, morning lectures and general sessions. Throughout the year, numerous regional meetings of Fellows and Associates have been conducted. Your president can testify to the professional and scientific excellence of some of those regional meetings which he was able to attend.

The College is quite alive to the new problems and new difficulties of physicians who are Fellows, Associates or potential material for the College, who are in the armed forces of the country. Already the Advisory Committee on Postgraduate Courses of the College carried out a week's program of Postgraduate Nights consisting of 16 lectures for the benefit of Medical Officers at one of the large Naval Hospitals. Discussions have taken place with the appropriate authorities of the Army and Navy who are very co-operative, and it is hoped that this program may be developed and expanded. It is not too much to expect that, when and where the military situations allow, medical service in military hospitals may be comparable to service in civilian hospitals. This will mean, of course, the best of medical care to the soldiers and incidentally (and it must be incidental) the professional progress of the medical officers.

Many Fellows and Associates of the College are on active military duty. For them the College has reduced the annual dues and initiation fees. The war activities of the individual members of the College, who may not be fortunate enough to wear uniform, are manifold. All over the country, Fellows of the College, in addition to their ordinary duties, are serving as examining physicians, are on draft boards, advisory boards and on appeal boards. As the war tempo increases, there will be more demands for double duty and makeshift duties. Many pet researches of our Fellows must be laid aside for the duration.

The National Research Council drafted members of the College as individuals for service on its many committees. A former President of the College, Dr O H Perry Pepper, is the hard working chairman of the Committee on Medicine of the National Research Council. I suspect that Dr Pepper is more in Washington than in Philadelphia.

Well over a year ago, the College undertook to classify internists for possible availability for military service, according to capabilities, experience, age and other criteria. Your President-Elect, Dr James E Paullin, of Atlanta, has devoted himself without stint to this arduous task. By this forehanded action and with similar activities by the American Medical Association and the American College of Surgeons, information concerning the Medical Resources of the country was available when war was declared. Now President Roosevelt has appointed Dr Paullin on all the important Committees of Procurement and Assignment. The Regents believe that the sum of \$3500 00 appropriated for clerical and technical assistance for this work has more than amply been justified in its value to National Defense.

Over a year ago when no governmental funds were available, because the Regents of the College and the National Research Committee on Medicine believed the need was urgent, the College made an appropriation of \$10,000 00 for the promotion of a research project of Dr Edwin J Cohn of the Harvard Medical School. This project concerned the preparation and adaptation of certain types of plasma for human transfusion. Dr Cohn has told us of some of his work at one of the morning lectures of this Annual Session. The necessary restrictions imposed by the state of war has, of course, prevented Dr Cohn from unfolding the whole fascinating story of his work. I like to think that these moneys are personal contributions of the Fellows of the College to National Defense, rather than the contribution of the College, which is impersonal.

Army medicine, naval medicine, aviation medicine, civilian medicine are in essence one and the same. Hence, in these Annual Sessions of the College, actually, as I have said before, a postgraduate week, there are papers in aviation medicine, on blood banks, on blood substitutes. There are papers on typhus fever, malaria, and tropical diseases. Such expert discussions have a direct relation to the war, the first group seemingly more than the second. But there will henceforth always be civilian aviation. Aviation is an important method of transportation today. There will be transfusion of blood and of blood substitutes in peace times. The medical problems discussed in all the clinics, panels, lectures and papers have application in both military and civil life. Yes, and I include geriatrics as a military problem. What makes a colonel or a general unfit at 60, or before 60, or not until 70? How can we select the men? And more important, how can we keep them fit? And, if this applies to the army, it applies peculiarly to the defense effort and it applies to civilians in times of peace. At this time the College has but a single purpose, that of winning the war, but the College believes that in war and in medicine, the secret of success is the offensive, the advance, the attack and always and ever so.

CLINICAL-PATHOLOGICAL CONFERENCE ¹

DISCUSSER—WALLACE M YATER, M D, F A C P, *Washington, D C*

PATHOLOGIST—CHARLES F BRANCH, M D, *Boston, Massachusetts*

DR YATER After having read the history of the case we are to discuss this morning, I am convinced that there are just as hard medical nuts to crack in Boston as there are in Washington and elsewhere I approach a discussion of this case with fear and trepidation, and hope it will not turn out to be a Dunkirk for me

May I suggest that we refresh our minds concerning this rather mystifying case by reading it over again together from beginning to end

CLINICAL HISTORY

The patient was a 35 year old man by occupation a wood-worker When he was 18 years old he had an attack of appendicitis with appendectomy under chloroform and ether anesthesia He had a prolonged convalescence from this operation with drainage of an appendiceal abscess On several occasions when the dressings were being changed and drains were inserted, chloroform anesthesia was necessary However, the recovery from this illness was said to be complete

Six years ago, when he was 29 years old, he had an attack of lobar pneumonia followed by a sterile pleural effusion which subsided after aspiration At about this time he commenced to have recurrent attacks of mild transitory jaundice

About a year ago he began having attacks of fever, usually accompanied by diarrhea There would be a sudden chill, high fever, and the passage of several loose stools The fever would last from 24 to 36 hours and then subside Between attacks of chills and fever and diarrhea he felt quite well At first the chills and fever occurred nearly every week He entered one of the Boston hospitals for study, remaining there for eight weeks Under observation he was found to have an irregular, low-grade fever which ranged between 98.6° F and 100° F, occasionally interrupted by chills when his temperature would be 102° F or 103° F

On physical examination the skin was normal in appearance The heart and lungs were negative except for a systolic murmur at the apex, no diastolic murmur was heard The spleen was palpable two fingers' breadth below the costal margin The rest of the physical examination was negative Numerous blood cultures were negative Agglutination tests for undulant fever and for typhoid and paratyphoid fevers were negative Gastrointestinal roentgen-ray series, films of the chest, intravenous pyelograms, and barium enema all were negative The electrocardiographic tracing showed slurring of the QRS complexes, suggestive of an intraventricular conduction defect On one occasion it was said that the patient had a shower of petechial hemorrhages over the skin, and in one blood smear a monocyte was found with an engulfed red cell In view of the extensive oral sepsis which the patient presented, numerous teeth were removed, but this procedure appeared to have no effect on either the chills or fever

The patient finally was discharged from the hospital, returning for follow-up study on two different occasions, one in two months and one six months later He

* One of the Clinical-Pathological Conferences given at the Annual Meeting of the College in Boston on April 22, 1941, under the direction of Dr Reginald Fitz

stated that he had been reasonably well after leaving the hospital except for one or two bouts of fever with the temperature going to 103° F

About six months after his last return to the hospital he entered the Robert Dawson Evans Memorial Hospital for further study. At this time he complained of recurrent attacks of chills and fever, and of a distended abdomen. The distention was of recent onset and caused no great discomfort.

The skin was pale and there were numerous telangiectatic spots over the arms and shoulders. Such spots typically had raised central areas which were red and from whose central point numerous small blood vessels radiated outward. When gentle pressure was exerted over these telangiectatic areas, pulsation of their smaller arterioles could be seen. The eye grounds were normal.

The lungs were clear throughout. The heart was not enlarged, there was a soft systolic murmur at the apex, but no diastolic murmur was heard. The blood pressure was 110 mm Hg systolic and 70 mm diastolic. The abdomen was slightly distended. The spleen was palpable in the left upper quadrant, extending 3 cm below the costal margin on deep inspiration. The liver was not felt. No other masses were palpable. There was a right-sided hydrocele and slight pitting edema over the ankles and sacrum.

The blood Wassermann reaction was negative, the hemoglobin was 70 per cent, with a red blood cell count of 3,500,000, the white cell count was 4,000, differential count of the leukocytes was normal. The nonprotein nitrogen ranged between 31 to 44 mg per cent, the blood cholesterol ranged between 250 to 300 mg per cent, the serum bilirubin ranged between 1.3 and 4.3 mg per cent. The sedimentation rate was elevated above normal. The Takata-Ara test was positive in all dilutions, the total protein of the blood was 5.7 gm per cent, of this the albumin was 2.5 gm and the globulin 3.2 gm per cent. Agglutination tests for the typhoid-paratyphoid group were negative. The bromsulphalein test showed 40 per cent retention of the dye at the end of half an hour with 50 per cent retention at the end of five minutes. Repeated examinations of the urine showed no albumin or sugar, bilirubin was present on six occasions, and urobilinogen always was increased in dilutions of 1:50 to 1:600, cultures of the urine were negative. Renal function appeared normal as judged by the phenolsulphonaphthalein test, there being an excretion of 67 per cent in two hours. Electrocardiographic tracings continued to show a constant slight intraventricular conduction defect. Roentgen-ray films of the heart and lungs were negative. The barium enema was negative.

The patient remained under observation in the hospital for 67 days, and during this time he had several sudden bouts of fever which lasted between 24 and 36 hours. On two different occasions during the period of fever, blood cultures were positive for colon bacilli. During the period of hospital observation the patient's abdomen became notably distended and there developed definite signs of ascites. The ascitic fluid removed had a specific gravity of 1.004, its protein concentration was 0.68 gm per cent, and of this the albumin concentration was 0.33 gm and the globulin concentration 0.35 gm per cent, the ascitic fluid sediment was negative. As a terminal event the patient developed tenderness in the left side of the neck with brawny induration and edema. This was associated with high fever, leukocytosis and delirium. At this time hemolytic streptococci were obtained from the throat on culture. The induration and edema in the neck continued to spread.

CLINICAL DISCUSSION

There are certain disadvantages confronting the discussor of a case with which he has had no personal connection. He has to accept the results of observations of others without having an opportunity either to check them

or to extend them. On the other hand, he has the definite advantage of seeing the case as a whole and not piecemeal as does the attending physician. This is the same advantage that a consultant often has over the general practitioner who has seen the development of a case in its early phases, who may have been confused by the early indefinite symptoms, and who perhaps may not have examined the patient sufficiently often as the illness developed.

Now in this case, I shall take advantage of my privilege by beginning my discussion of the case near the end of its course. The data in the second from the last paragraph of the clinical history indicate definitely that the patient finally developed advanced disease of the liver, as indicated particularly by the retention of bromsulfalein, the positive Takata-Ara test, and the increase in the amount of urobilinogen in the urine. The bromsulfalein test, when positive, is quite specific as an indicator of advanced liver disease when there is little or no jaundice. The Takata-Ara test, though not specific, is quite suggestive of cirrhosis of the liver, when positive. A definite increase in the urobilinogen output is quite definitely an indication of hepatic disease. Other findings which support the diagnosis of serious disease of the liver, and particularly cirrhosis, are the anemia, the leukopenia, the moderately elevated blood cholesterol, the reversal of the albumin-globulin ratio, the fluctuating level of the serum bilirubin with moderate increase, and the later development of definite signs of ascites. The spleen was also palpable, and moderate splenomegaly is common with cirrhosis of the liver. The liver could not be felt and may, therefore, well have been shrunken. The presence of a hydrocele and slight pitting edema of the ankles and sacrum are consistent with the diagnosis of cirrhosis of the liver, and are no doubt due largely to the depression of the serum albumin level. On his last admission it was noted that there were numerous telangiectatic spots over the arms and shoulders. A description of these lesions indicates that they were the so-called spider nevi, which, when present, are practically pathognomonic of cirrhosis of the liver. Examination of the ascitic fluid indicated that it was a transudate and not an exudate.

The last paragraph of the clinical history shows that the final episode in this patient's life was his development of an intercurrent infection, consisting of two phases: colon bacillus bacteremia, and finally a cellulitis of the neck. It is, of course, not unusual for patients with cirrhosis of the liver to develop an infection terminally, which their lowered resistance does not allow them to overcome.

Having established the point that the patient's illness terminated with cirrhosis of the liver and the terminal intercurrent infection, let us return now to the history of the case, to see whether we may determine the cause and type of this cirrhosis. The patient was a wood-worker, but the history does not state what type of wood-worker. So far as I know, there is nothing in the occupation of wood-workers that could remotely lead to cirrhosis of the liver. However, the history states that chloroform anesthesia was

used several times for surgical purposes when the patient was 18 years of age. Recovery, however, was complete, and although chloroform sometimes produces serious liver damage, it is the type of liver damage from which recovery is complete unless the patient succumbs to it soon after the administration of the chloroform. Furthermore, the patient's chronic illness which led to his death did not apparently begin until 11 years later, when he was 29 years old. Therefore, I believe we can safely rule out the use of chloroform in the etiology of the disease of the liver.

Six years before the patient died, when he was 29 years old, he had an attack of lobar pneumonia, soon after which he began to have recurrent attacks of mild transitory jaundice. The etiology of the pneumonia is not stated in the history. However, streptococcal pneumonia and pneumococcal pneumonia are both occasionally complicated by cholangitis, and since the pneumonia was the only definite infectious disease from which the patient suffered, which might have played a rôle in the etiology of the disease of the liver, the possibility that it was important in this connection cannot be overlooked. Therefore, I believe we should assume that the patient may have developed a low-grade chronic cholangitis as a result of his pneumonia.

Certainly the subsequent course of the patient's illness following the pneumonia, particularly during his last year of life, was very suggestive of chronic cholangitis. He had exacerbations of the chronic infection, associated with sudden chills, high fever, and diarrhea. Diarrhea sometimes occurs in connection with cholangitis. Between these brief exacerbations the patient was quite well, but while under observation for eight weeks in one of the Boston hospitals it was noted that he had an irregular low-grade fever even between the more severe episodes.

The fourth paragraph in the history is designed to confuse us, not consciously on the part of the historian, but because of the facts contained therein. A systolic murmur at the apex was noted, but apparently without cardiac enlargement. The murmur itself need not be important. The spleen was noted to be palpable. This finding may be present with many infectious diseases, one of which is bacterial endocarditis. However, numerous blood cultures were negative, and there were no other features to suggest that diagnosis. Agglutination tests for certain of the prolonged fevers were negative. Diseases of the gastrointestinal tract, lungs, and urinary tract were ruled out by roentgen-ray and other studies. The electrocardiograms, to which we do not have access, showed slurring of the QRS complexes, but this finding in itself is of no importance in the consideration of our case, since it may occur under many circumstances. The one shower of petechial hemorrhages over the skin should not confuse us, since it was a transient episode, and one that might occur in many conditions. The removal of numerous teeth without effect upon the chills or fever was merely another instance of the fallacy of our theory of focal infection, which is beginning to "go by the board."

The course of the illness continued much the same way throughout, with longer or shorter remissions, until the terminal phase marked by the presence of advanced disease of the liver

We have now come to the point where it is necessary to tie up our diagnosis of cirrhosis of the liver with the history of long-standing infection and bouts of chills, fever, and diarrhea. Laennec's cirrhosis does not follow such a clinical course, but there is a form of biliary cirrhosis, quite rare, which has been called cholangitic induration of the liver, or cholangitic cirrhosis. It is not the result of obstruction of the extrahepatic bile ducts but of chronic recurrent intrahepatic cholangitis. In this condition the liver becomes smaller and firmer and its surface more or less granular. When the liver becomes greatly shrunken by the periportal fibrosis, a secondary result of the shrinkage is portal congestion, and then splenomegaly and even ascites may appear. I believe that this case fits well the description of this rare disease.

In conclusion, I believe we can predict, if our ratiocination is correct, that the pathologist will show us a small, hard, granular liver, which microscopically shows an extreme degree of fibrosis primarily involving the intrahepatic biliary tract, but secondarily causing obstruction also to the portal radicles. There should be very little functioning liver parenchyma left.

PATHOLOGICAL DISCUSSION

DR. BRANCH

The pathologist accustomed to viewing the cumulative result of years of disease not infrequently finds it difficult to assess with mathematical accuracy all of the facts before him. Even with the aid of a complete clinical history and the facts marshaled by long microscopical study, one frequently finds that all is still not clearly explained. To one with such experiences behind him, Dr. Yater's brilliant and clairvoyant discussion is most refreshing, and I am given to wonder if the good internist was not looking over my shoulder at the necropsy. His analysis is so perfectly accurate down to the last detail that it must perforce bespeak his great clinical ability.

As has been so carefully differentiated, the patient had no intrinsic heart disease, clinical signs and symptoms to the contrary notwithstanding. The heart weighed but 210 grams and showed no gross pathological changes. There was no histological evidence of rheumatic fever or other pathologic findings of consequence.

The lungs were also essentially negative, presenting only a slight terminal hypostatic pneumonia. A partially obliterative fibrous pleuritis on the right attested the pleural effusion which was a sequel to his pneumonia six years ago.

The gastrointestinal and genitourinary systems were essentially negative.

As pointed out, patients with cirrhosis frequently become so debilitated that their resistance is lowered and terminal bacterial invasion is frequent. In this instance the terminal *Bacillus coli* bacteremia and the cellulitis of the

neck were such manifestations. The importance of the bacteremia is difficult to estimate for it had given rise to no demonstrable focal lesions. The cellulitis of the left side of the neck with formation of an abscess about the left lobe of the thyroid yielded *Streptococcus hemolyticus* but no *Bacillus coli*. The carotid sheath was involved in this process, and there was also a small streptococcus-containing abscess just behind the sternal notch.

The splenomegaly of 400 grams, which could be palpated 3 centimeters below the costal margin, was primarily the response to a simple passive congestion due to the advanced liver obstruction. However, it also showed a well defined acute splenitis commensurate with the degree of cellulitis in the neck.

The extrahepatic biliary system and the pancreas were entirely negative. The gall-bladder contained no stones, all ducts were patent and showed no evidence of thickening or occlusion.

With all the clinical evidence at our disposal, one can hardly escape the outstanding picture of profound chronic liver disease. We have been much impressed with the development of this angle of the case by the discussor and heartily concur in the many aspects of his clear differential diagnosis. The chloroform episode was obviously a "red herring." The development of intermittent jaundice following the patient's pneumonia is much more suggestive of the true nature of his liver pathology. As has been so neatly drawn to your attention, during the past year at least, the patient has suffered from a marked chronic cholangitis.

With this outline so sharply stenciled on your canvas, little remains for me to do but fill in the colors. The liver presented a truly remarkable picture. It weighed but 775 grams, yet presented none of the external characteristics of the healed stage of acute yellow atrophy or toxic cirrhosis. It was extremely firm, relatively regular in outline and in general was pale yellowish-brown. Its entire surface was diffusely and uniformly studded with myriad minute, bright orange-brown nodular elevations, averaging 2 to 3 millimeters in diameter. The intervening capsule showed a dense fibrous thickening, and no normal lobulations could be discerned. Because of its density the organ was sectioned with difficulty. Multiple serial sections reveal the entire liver uniformly replaced with myriads of minute, golden-brown, plateau-like elevations 3 millimeters in diameter, roughly corresponding to the normal lobulations. The intervening stroma was depressed and consisted of glistening gray fibrous tissue. The interlobular bile ducts were thickened and projected slightly from the surrounding fibrous tissue. They were rather sharply defined by their contents, which consisted of granular, cloudy, pale greenish-brown, mucoid bile. There was no gross evidence of bile stasis in the smaller canaliculi.

Histologically, the picture was entirely typical of the entity described by Dr. Yater. The outline of the original lobules was well preserved, and, if anything, accentuated by a marked increase of connective tissue in the periportal canals. The remaining parenchyma was arranged in a normal

fashion about the central veins, and in general consisted of liver cords which were hyperplastic. At some points they showed various stages of degeneration, whereas in other regions they were definitely regenerating. Near the periphery of some lobules were minute areas of focal necrosis, in which two or more liver cells were being invaded by neutrophiles. At the periphery the lobules were gradually destroyed by the recurrent acute attacks, so that now the portal canals are replaced by bands of connective tissue, actually 1 to 2 millimeters in width. These old battlefields contained all sorts of mementos of previous engagements. The scarring was profound. Large numbers of lymphocytes, plasma cells and monocytes infiltrated this entire zone, and the progressive nature of the lesion was further indicated by large periductular accumulations of neutrophiles and a rare eosinophile. The larger ducts were relatively constricted by the surrounding infiltration and scar tissue, and their lumina contained the partially inspissated, semipurulent bile noted above. The smaller bile ducts gave an erroneous impression of being increased in number, their epithelium was intact and they were virtually occluded by the surrounding induration. The intralobular canaliculi showed more evidence of bile stasis than was suggested by the gross picture, but in nowise comparable to the degree of dilatation observed in a true obstructive biliary cirrhosis. There was no central necrosis nor any pathologic change compatible with the suggested injury created by chloroform poisoning.

Thus, we have a liver showing a true cholangitic induration, or if you wish, an infectious biliary cirrhosis, a liver which in the early stages of the disease was larger than normal and at that time would have shown an acute infectious hepatitis, one which now is a rock-like monument to successive waves of exacerbation and remission, each receding line clearly marked in its remaining and totally insufficient architecture.

In closing we must admit that the microscope did no more for us, nor brought us no less certainly to the correct conclusion than did the illuminating remarks of the discussor.

PRIMARY CARCINOMA OF THE LUNG (REPORT OF 115 CASES, 38 AUTOPSIES AND 77 BRONCHOSCOPIC BIOPSIES) *

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ROSAHN ¹ states that definite criteria for diagnosis should be established to render valid any comparisons of the incidence of carcinoma of the lung at different periods These criteria are

- 1 An autopsy must have been performed
- 2 The carcinomatous nature of the lesion must have been verified microscopically
- 3 There must be no reasonable doubt that the neoplasm was a primary growth
- 4 Percentage should be calculated on the basis of total adult necropsies Rosahn arbitrarily adopts 20 years as the lower age limit

In our report we have attempted to fulfill all of the above criteria We have an autopsy series of 38 primary carcinomas of the lung occurring in the years 1911-1939 inclusive, and 77 cases of bronchoscopic biopsies during 1933-1940, in which a pathological diagnosis of carcinoma was made

INCIDENCE

Simons ² in his monograph has reached the following conclusions regarding incidence

- 1 Incidence of the disease has increased absolutely and relatively
- 2 Continued suggestions that such an increase is only apparent and not real are denied by the facts
- 3 The increases were gradual until the early 1900's, since when the gradient of increase has become constantly steeper
- 4 In many localities the greatest incidence seems to have been reached in 1924, whereas in others the frequency still is advancing

In general it can be stated that 1 to 2 per cent of necropsies reveal lung cancers and that 10 per cent of all cancers at autopsy are lung cancers

All these factors concerning incidence are, in general, borne out in our group of cases For example in table I we see the great increase in lung cancers whereas carcinomas of the stomach and colon were remaining relatively constant

* Received for publication August 17, 1940

From the Departments of Bronchscopy and Pathology, Mercy Hospital, Pittsburgh, Pa

TABLE I

Year	Ca of Stomach	Ca of Colon	Ca of Lung	Total Autopsies
1911-21	21 or 3.4%	7 or 1.1%	5 or .81%	614
1922-32	14 or 3.5%	14 or 1.2%	17 or 1.5%	1,158

From 1911-1939 there have been 2,694 necropsies at the Mercy Hospital, of these there has been a total of 359 carcinomas. This would then make lung carcinoma 13 per cent of all carcinomas. This figure coincides rather closely with that generally given.

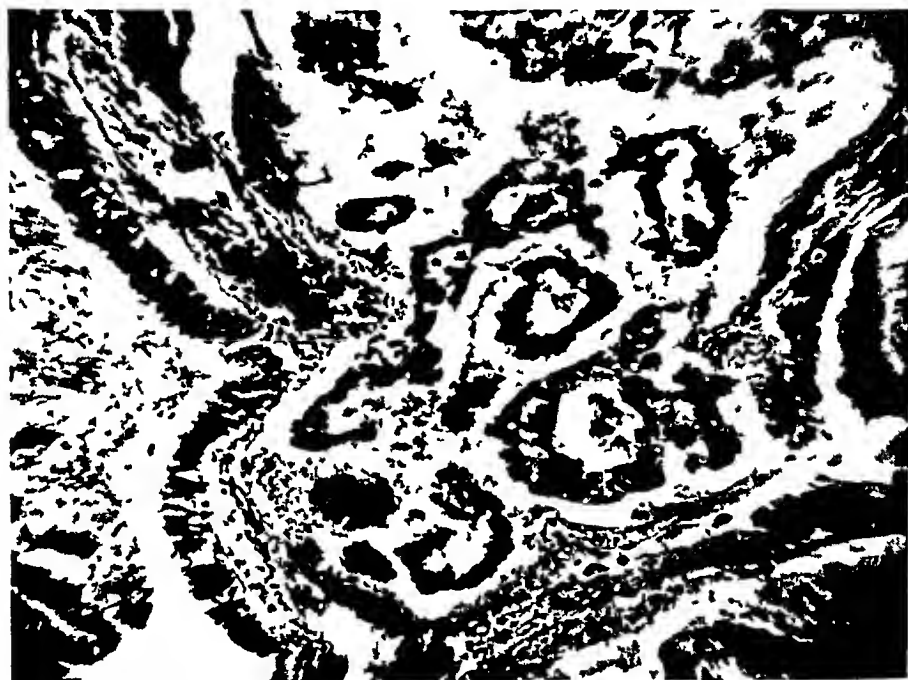


FIG 1 Adenocarcinoma type ($\times 125$) Glandular structures shown beneath the epithelium lining a bronchus. Note: This patient was a fireman. He dated the onset of his symptoms from a fire during which he inhaled a great deal of smoke. This was a year before admission.

ETIOLOGY

The etiological factor here as in other carcinomas is still a mystery. The various factors suggested are heredity, trauma, pulmonary tuberculosis, influenza, pneumoconiosis, chronic pulmonary diseases, roentgen-ray, dust inhalation, tin particles, motor exhaust fumes, war gases, occupational hazards, tobacco smoking. Simons² concluded that no single etiologic agent could be pointed out as the cause of pulmonary cancer. He states, "In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only conclusion possible is that such irritation is the real activating or causative factor in the disease. This is not to say, of course, that all chronic pulmonary irritations

ensue in carcinomas, and it is to be hoped that future research will make this definition of the cause either more specific or more conclusive or both "

TABLE II
Autopsy Series

Previous Respiratory Infection	Number	Percentage
Asthma	1	2.6
Bronchiectasis	1	2.6
Bronchitis	3	7.8
Influenza	3	7.8
Pneumonia	4	10.5
Tuberculosis	1	2.6
No previous respiratory infection	25	65.7
Total	38	

Note: Two cases had lung abscess. One case had active tuberculosis.

Bronchoscopic Series

Previous Respiratory Infection	Number	Percentage
Bronchitis	3	3.7
Diphtheria	1	1.4
Influenza	8	10.5
Pleurisy	1	1.4
Pneumonia	20	25.8
No previous respiratory infection	44	57.2
Total	77	

TABLE III

Autopsy Series			Bronchoscopic Series		
Tobacco Smokers	Number	Percentage	Tobacco Smokers	Number	Percentage
Heavy	2	5.2	Heavy	16	20.7
Moderate	4	10.5	Moderate	22	28.5
Not smokers	32	84.2	Not smokers	39	50.6
Total	38		Total	77	

Wells and Cannon⁷ report a case in which localized trauma appeared to be the exciting factor in the production of a lung cancer.

In our study we have been unable to find any specific etiologic factor. Some investigators have considered influenza as an etiologic factor but we would raise the question whether or not the manifestations of influenza may not often be an early sign of the pulmonary tumor. The occupations of our patients are listed in table 4.

Sex Incidence. In general, as reported by Overholt,⁴ there are three males to every female. This has remained fairly constant in spite of the increased tendency of women to smoke. In our autopsy series we have had 34 males and 4 females, and in the bronchoscopic series we have had 61 males and 16 females.

TABLE IV

Autopsy Series		Bronchoscopic Series	
Occupation	Number	Occupation	Number
Business man	1	Barber	2
Carpenter	4	Brass worker	1
Chipper steel mill	1	Butcher	1
Coal miner	2	Clerk	5
Electrical craneman	1	Clothes presser	1
Envelope cutter	1	Construction worker	1
File clerk	1	Cook	1
Fireman	1	Electrician	1
Garage man	1	Engineer	1
Housewife	1	Florist	1
Janitor	1	Glass worker	1
Laborer, steel mill	1	Housewife	15
Mill foreman	1	Laborer	8
Minister	1	Machinist	4
Open hearth worker	1	Merchant	2
Oyster opener	1	Metal worker	2
Painter	1	Mill worker	1
Scrapman	1	Miner	8
Store keeper	1	Painter	2
Transfer bus	1	Physical education instructor	1
Transportation Co official	1	Postmaster	1
Traveling salesman	1	Printer	1
Truck driver	1	Produce peddler	1
Unknown	11	Retired	12
		Salesman	2
		Tanner	1
Total	38	Total	77

TABLE V

Autopsy Series			Bronchoscopic Series		
Sex	Number	Percentage	Sex	Number	Percentage
Male	34	89.5	Male	61	79.3
Female	4	10.5	Female	16	20.7
Total	38		Total	77	

Age Incidence There have been about 13 cases reported in the literature occurring below the age of 19. The youngest we have been able to find is a questionable case occurring in a child of seven. Our youngest patient was 23 and the oldest 76.

TABLE VI

Autopsy Series			Bronchoscopic Series		
Age	Number	Percentage	Age	Number	Percentage
20-30	0	0.0	20-30	2	2.3
30-40	4	10.5	30-40	5	6.5
40-50	10	25.5	40-50	10	12.9
50-60	15	39.5	50-60	30	38.9
60-70	6	15.5	60-70	24	31.4
70-80	3	9.0	70-80	6	7.7
Total	38		Total	77	

FIG 2 Small round cell type ($\times 125$)

negro population at our hospital. D'Aunoy,⁶ in a series of 74 autopsies from the Charity Hospital in New Orleans, reported 47 white patients and 27 negroes. There is of course a much larger negro population at that institution. In general we believe that lung carcinoma is relatively rarer in the colored race.

TABLE VII

Age

PATHOLOGY

There have been numerous classifications of lung carcinoma based on the macroscopic appearance. Grossly, the tumor occurs most commonly as an infiltrating type of lesion usually beginning at the hilus and extending through the lung parenchyma. There are two other general types, one a diffuse growth resembling a pneumonia or miliary tuberculosis, the other, the multiple nodular type in which the primary tumor may be minimal with wide-spread metastases both in lungs and elsewhere.



Fig 3 Large polyhedral cell type ($\times 125$)

The masses of tumor tissue are usually gray, white or pink on cross section. Often one finds many necrotic areas filled with material resembling pus or mucus. This is often mistaken for tuberculosis or even pneumonia.

To quote from Simons² "In the earliest stages, according to Tuttle and Womack, one sees a piling-up of the mucous membrane with a gradual extension along the mucosa and out into the bronchial lumen. The picture becomes one of a fanshaped grayish mass extending out into the lung parenchyma with various stages of necrosis and abscess formation. Less often one sees the tumor as a diffuse growth involving an entire lobe or even a whole lung, thus giving a picture not unlike that seen in the gray hepatization of pneumonia. Rarely the tumor may be found as single or multiple nodules in the parenchyma of the lung with no apparent connection with the larger bronchi."

The most common associated lung changes in Arkin and Wagner's⁸ series of 74 cases (Simons), were pleural effusion (47 per cent), bronchiec-

tasis (43 per cent), acute pneumonia (28 per cent), chronic pneumonia (20 per cent), abscess or gangrene (20 per cent) and purulent bronchitis (19 per cent). The manifestations of pulmonary carcinoma clinically and pathologically are so diverse that the diagnosis is difficult. As Hruby and Sweany⁶ have stated, tuberculosis is the most common disease confused with primary carcinoma of the lung.

In general, the bronchial origin is demonstrable according to most investigators in about 70 per cent of cases. Sweany⁶ has stated, "If there



FIG 4 Oat cell type ($\times 125$) Nests of tumor cells are shown in a loose stroma beneath a layer of bronchial epithelium

is any merit to the theory of origin from bronchial mucosa it will necessitate the proof of some form of metaplasia from one type of tissue to another." An injury to bronchial lining usually heals. If a malignant tendency exists, carcinoma may result and there seems to be a multiple potential nature in the basal cells. Cancers arising from the pulmonary alveoli are very rare, if they exist at all. There is still some question as to whether the lining of the alveoli is epithelial or mesothelial. We feel, as most investigators do, that the latter is true. Womack⁷ has stated that carcinomas which arise in the periphery of the lung are more rapidly fatal than those arising at the hilus. He explains this on the basis of more rapid spread by way of lymphatics to the hilar nodes.

The present accepted theory of origin of the various cell types of lung carcinoma is that of Fried⁸ (Simons). He summarizes his belief by stating that of the cells lining the bronchial mucosa, that is, the ciliated columnar,

the goblet, and the "basal" cells, only the last are concerned in the process of regeneration of the bronchial mucous membrane. It is evident, therefore, that these cells likewise serve as a sole matrix for primary bronchiogenic tumors. And third, primary squamous cell epitheliomas and basal cell epitheliomas of the lungs do not result from metaplasia of preexisting ciliated columnar epithelium, but originate through protoplasia or indirect metaplasia of the undifferentiated basal cell of the bronchial mucous membrane. D'Aunoy⁷ chooses to call the undifferentiated basal cell the "reserve cell." We have divided our cases into adenoid, squamous, and undifferentiated types. In the latter we have described basal cell, round cell and large polyhedral cell types.

TABLE VIII
Autopsy Series

Cell Type	Number	Percentage
Adenoid	7	18.4
Squamous	9	23.6
Undifferentiated		
Large polyhedral	4	10.5
Oat cell	12	31.5
Round cell	6	15.7
Total	38	

Note. In many of the tumors there was a mixture of various cell types. The above classification is made on the predominant type of cell. Two of our autopsy cases were originally diagnosed in 1916-17 as lymphosarcoma. A review of the slides shows that these were actually primary carcinomas of lung. This was formerly a rather common error in diagnosis.

Bronchoscopic Series

Cell Type	Number	Percentage
Adenoid	3	4.0
Squamous	28	36.3
Undifferentiated		
Large polyhedral	13	16.8
Oat cell	24	31.2
Round cell	9	11.7
Total	77	

METASTASES

The usual order of frequency is (1) regional lymph nodes, (2) liver, (3) lungs, (4) bones, (5) kidneys, (6) adrenals, (7) pleura, (8) brain, (9) pericardium, (10) pancreas, (11) cervical lymph nodes, (12) heart, (13) thyroid, (14) spleen. Metastases occur by blood and lymph stream. One factor supporting blood stream metastasis is that breast and pulmonary carcinomas furnish the highest percentage of secondary new growths in the cranial cavity.

It has been stated in general that the right lung, especially the upper lobe, is most frequently involved. This is also apparently true in pulmonary tuberculosis. The reason for this is not evident. The fact that this portion of the lung is most subject to irritative factors may have some significance.

TABLE IX
Autopsy Series

Metastases	Number
Regional lymph nodes	22
Peribronchial	13
Mediastinal	4
Supraclavicular	4
Retroperitoneal	4
Mesenteric	13
Liver	12
Pleura	10
Pericardium	8
Opposite lung	6
Subcutaneous tissue	6
Kidney	5
Heart	5
Pancreas	4
Adrenal	4
Diaphragm	3
Aorta	3
Esophagus	3
Spleen	2
Trachea	2
Gall-bladder	2
Bone	2
Thyroid	1
Brain	1

Note There was one case in which the spinal fluid suggested brain metastasis, but permission was not granted for prosection of the head In another case permission was granted only for examination of the lung

TABLE X
Autopsy Series

Frequency of Side Involved	Number	Percentage
Right lung	25	65.7
Left lung	13	34.2
Total	38	

Note There was also a tendency in our series to find the upper lobes involved more frequently than the lower Thirty-six of our cases showed the infiltrating type of lesion One was a diffuse adenocarcinoma resembling gray hepatization and one was a multiple nodular type

Bronchoscopic Series

Frequency of Lobes Involved	Number	Percentage
Right main bronchus	6	7.7
Left main bronchus	7	9.7
Right upper lobe	13	16.6
Left upper lobe	1	5.2
Right lower lobe	31	44.1
Left lower lobe	9	11.6
Both lower lobes	1	1.4
Right middle lobe	2	2.3
Right middle and lower lobes	1	1.4
Total	77	

BRONCHOSCOPIC FINDINGS

Bronchoscopy is the one certain method by which carcinomas of the lung can be diagnosed early Nearly 80 per cent of the primary lung carcinomas are situated in one of the main bronchi in which visualization is within range

In these, a biopsy can be taken with ease. In many of the remaining cases, if no growth is seen within the bronchus, one can make an almost certain diagnosis if there is fixation of the involved bronchus.

Bronchoscopy is a safe procedure when performed by a trained endoscopist. No patient who presents a dry cough, wheezing or shortness of breath should be denied a bronchoscopic examination regardless of whether he is in the cancer age or not. Often with minimal physical signs and neg-



FIG 5 Squamous cell type ($\times 125$)

ligible roentgen-ray findings, one is amazed to find an early carcinoma of the lung. It is only in such cases that we may be able to cure those afflicted with this increasingly prevalent malady. One negative biopsy report does not exclude the possibility of carcinoma. If the endoscopist feels that the growth looks malignant, he should repeat the examination and remove more tissue for further histologic study. This should be repeated as often as feasible until a diagnosis is established. Too often the acceptance of one negative biopsy report results in the later appearance of an inoperable carcinoma.

Bronchoscopy is a great aid to the thoracic surgeon in helping to localize the lesion and in determining the operability of a given tumor. If the bronchus is fixed, it indicates that mediastinal involvement has taken place, or if the tumor extends into the trachea, surgical removal is precluded. If a suppurative lesion has occurred distal to the growth (many times these patients are sent to the hospital with a diagnosis of lung abscess), the endo-

scopist can aspirate the infected material and also dilate the bronchus in order to facilitate better drainage

Bronchiography with the injection of iodized oil through the bronchoscope or with the catheter may aid in localizing tumors out of the range of bronchoscopic vision

PHYSICAL SIGNS

Physical findings are so variable that they may simulate any type of pulmonary lesion. In our cases 97 per cent showed clinical manifestations

ROENTGENOLOGIC STUDIES

Roentgenologic changes were noted in approximately 99 per cent of the cases in our series. As noted by other writers, the characteristic finding was evidence of atelectasis of lung. Evidence of superimposed inflammatory reactions was noted in about 27 per cent of the cases. An absolute roentgen-ray diagnosis of carcinoma of lung cannot be made. It can be used only as a diagnostic aid.

SYMPTOMS

The four cardinal symptoms found in our group were cough, hemoptysis, pain and dyspnea. In conjunction with these fever, chills, weight loss, wheezing and asthma were found in many of the cases.

TABLE XI

Symptoms	Number
Cough	43
Hemoptysis	16
Pain	30
Dyspnea	18

Cough is by far the most common symptom. At the onset in most cases it was dry and non-productive. Subsequently it often became productive of a clear, odorless, mucoid sputum. Later the sputum became blood streaked, with frank hemoptysis being noted in many cases. Those cases in which bronchial obstruction had resulted in abscess formation had a purulent sputum. Hemoptysis was usually characterized by bright red streaking of the sputum. Later in the disease the expectoration of old blood of a brownish-red color was noted. Dyspnea and wheezing are usually early symptoms of "stem-bronchus" involvement. Fever was found late in the disease when obstruction had begun to occur with formation of abscesses. This was found more frequently in "stem-bronchus" involvement. Pain, in the form of an uncomfortable sensation in the chest, is often present early in the disease, but severe pain is found late when metastases have occurred.

TREATMENT

Prior to the advent of thoracic surgery, the only weapons available for treatment of carcinoma of the lung were radium, roentgen-ray, and fulguration. Fulguration was usually done endoscopically but it was an unsatisfactory procedure because excision is impossible and the risk of hemorrhage is great. Many writers in years past have reported cases in which they claim to have obtained complete cures of carcinoma of the lung by this method, but from our present-day knowledge of the subject of carcinoma of the lung, one may well doubt whether they were dealing with actual carcinoma or with some inflammatory lesion. This method has been more or less completely discarded.

Radium implantations have been attempted and in some cases, if the lesion is easily accessible with the bronchoscope, one might consider this method before attempting radical surgery. This method was attempted in one of our cases for the reason that the lesion was early and the patient was 77 years of age. Thoracic surgery was out of the question, and since the lesion was early and at the same time involved the right stem bronchus, we concluded that we could give her palliative treatment in this manner. She lived for three years before the tumor began to grow rapidly with eventual fatality. In two other cases radium implantations were attempted owing to the patient's advanced age, but with scant therapeutic effect.

We have found roentgen-ray treatment to be of very little value. We are inclined to agree with Overholt, who believes that since most of these lesions are situated in main stem bronchi, one must do damage to normal tissues in order to destroy the tumor growth. In our series 15 cases were treated by deep therapy with no apparent benefit. In addition we found that it tended to produce inflammatory reactions, and to result in many systemic reactions such as loss of appetite, nausea and vomiting.

The treatment of carcinoma of the lung has finally evolved into surgical removal of the involved portion or whole lung. With the great improvement in the technic of thoracic surgery, the operative mortality has decreased in the last 10 years to an acceptable figure. Unfortunately, in our series, the cases suitable for surgical intervention were few. One left pneumonectomy was performed, and the patient is still living three years after operation. Two lobectomies were performed. One patient died six months after operation as a result of pneumonia, the other died three months after operation due to metastases, which were not demonstrable previous to operation. The important thing is to make an early diagnosis so that the case will be amenable to surgical treatment. The family physician should realize that any obscure pulmonary lesion requires thorough study until a definite diagnosis has been established. This has been well illustrated in our series of cases in that in only three cases out of 77 could surgery be considered. A great deal of progress can be made in this disease when we have succeeded in forming a capable, cooperative unit consisting of family physician, internist, roent-

genologist, bronchoscopist, surgeon, and pathologist When this is achieved early diagnosis and successful treatment will be accomplished

FOLLOW-UP OF BRONCHOSCOPIC CASES

All of the 77 cases herein presented died within 3 to 18 months after the diagnosis had been made except the single one that is still living three years following pneumonectomy In a small number of these cases the diagnosis has been verified at autopsy There are several cases living and well two years following a positive diagnosis of carcinoma of lung on tissue obtained by bronchoscopic biopsy These have not been included in this series The diagnosis of tissue obtained by the bronchoscope is very difficult in many instances It is only by repeated and frequent examinations of such tissues that the pathologist will be able to make the correct decision in border-line cases

CONCLUSIONS

1 We have presented a series of 115 primary carcinomas of the lung Thirty-eight of these were autopsy cases Seventy-seven were diagnosed by means of a bronchoscopic biopsy

2 There has been a relative and an absolute increase in incidence In our series primary lung cancer accounted for 13 per cent of the total number of carcinomas

3 Cough, dyspnea, hemoptysis and pain are the four cardinal symptoms of carcinoma of the lung

4 Bronchoscopic examination is by far the most important diagnostic procedure available and should be done in all cases of persistent cough whether dry or productive

5 Of 77 cases diagnosed by bronchoscopic examination, only three cases were amenable to surgical treatment

6 Of 77 cases, 76 were dead within three to 18 months from the time the diagnosis was made

7 Lobectomy or pneumonectomy in suitable cases is the treatment of choice

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THE VALUE OF SPLENECTOMY IN FELTY'S SYNDROME¹

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CHAUFFARD and Ramond described the association of chronic infectious arthritis and lymphadenopathy in 1896¹. They believed that the hemopoietic system was involved in these cases. One year later Still² described a deforming type of infectious arthritis in children associated with splenomegaly, lymphadenopathy, leukocytosis and anemia. Herringham³ de-

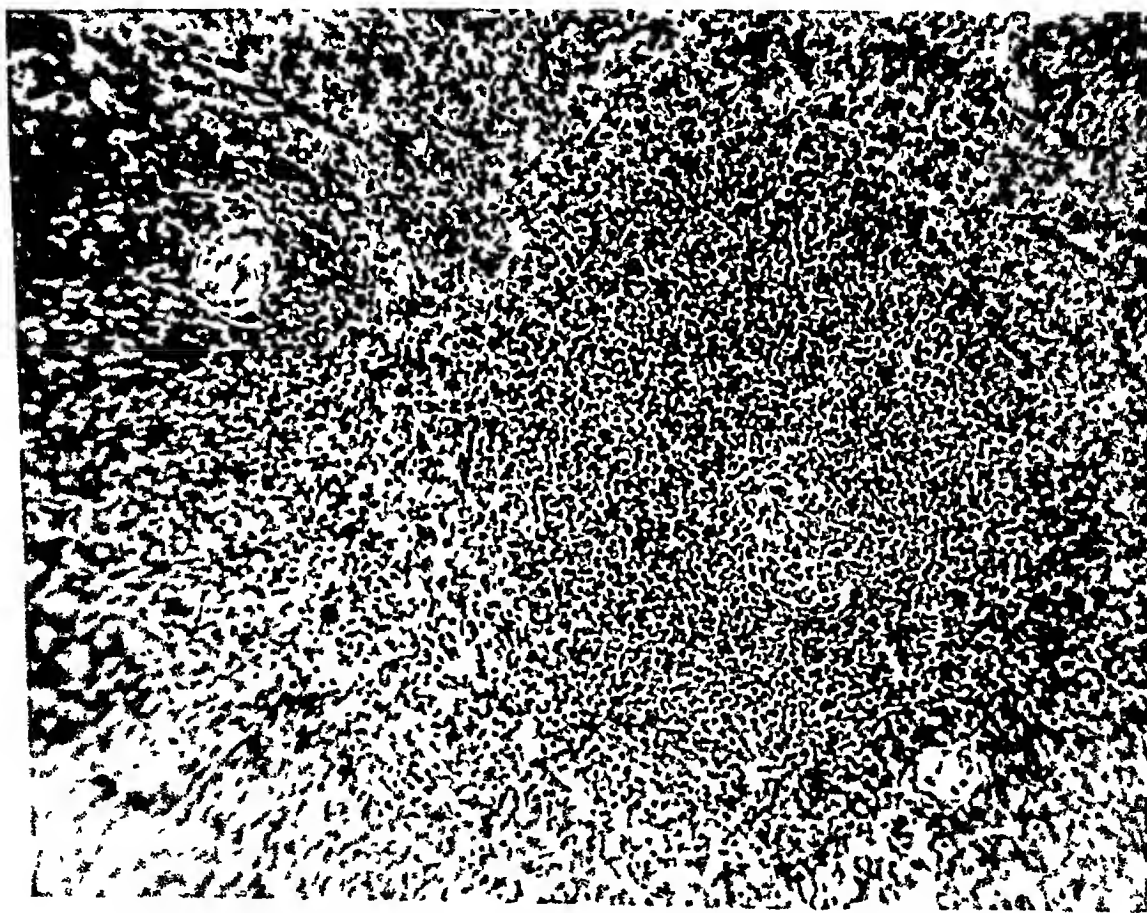


FIG. 1. Case M. Y. Low power photomicrograph of spleen showing large Malpighian corpuscle. Hematoxylin-eosin. $\times 155$.

scribed a case of polyarthritis in a 15 year old boy, associated with a leukocytosis of 11,200, a color index of 0.7 (hemoglobin of 50 per cent), an enlarged spleen, and an enlarged liver. He concluded that the syndrome, described 112 years previously by Still and atrophic arthritis were the same disease.

The gap in the bridge was closed by Felty in 1924. He⁴ described a form of arthritis in the adult which was characterized by polyarthritis of the atrophic variety, fever, secondary anemia, leukopenia, splenomegaly and tachycardia. He described five cases, all of whom had arthritis of at least two years' duration. However, "in contrast to the prolonged course of the disease, and the ubiquitous distribution of pain which is the presenting symp-

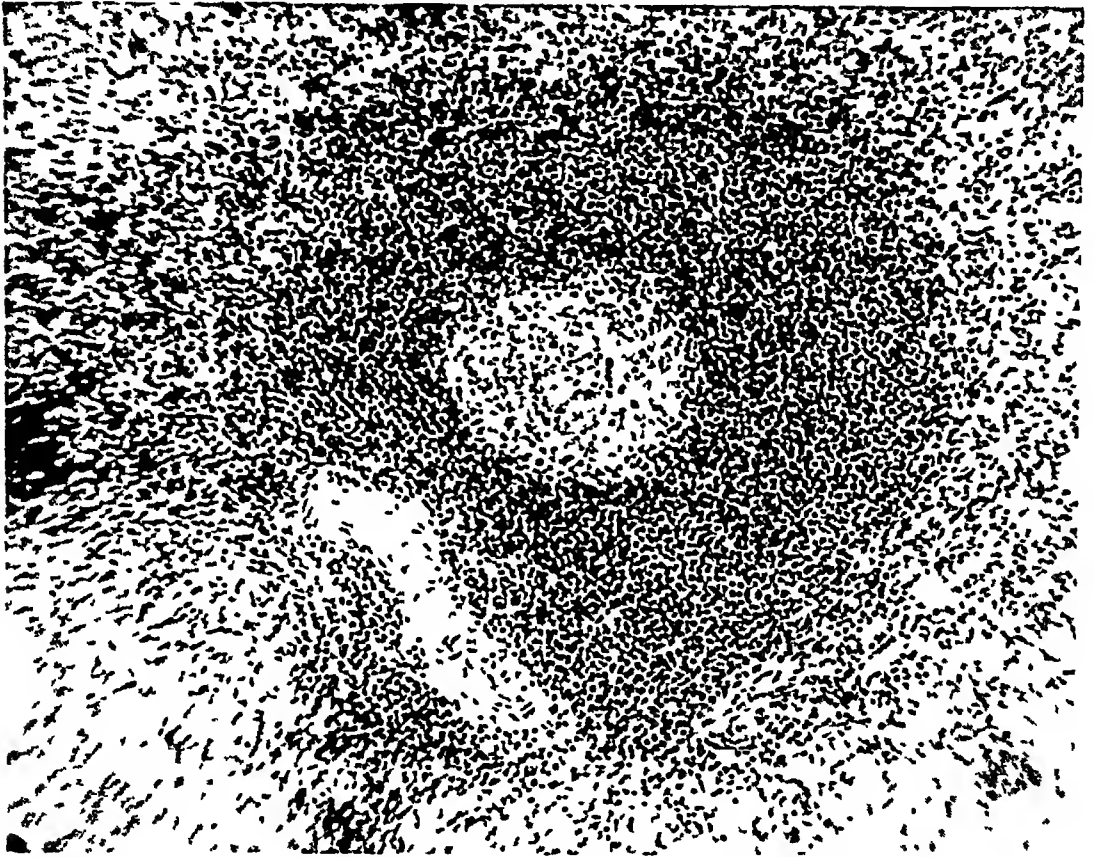


FIG 2 Case M Y Low power photomicrograph shows a dilated splenic sinus, the rich cellular nature and the large germinal center of the Malpighian body. Hematoxylin-eosin. $\times 155$

tom in all the patients, the objective findings both by physical and roentgenographic study are neither widespread nor indicative of a very damaging or destructive process." The average age of the five patients was 50 years, the range being 45 to 65. All the patients had lost considerable weight (40 to 65 pounds) since the onset of the illness. The spleen was palpably enlarged, firm and nontender in all cases. All had leukopenia, ranging from 1,000 to 4,200 leukocytes. Slight secondary anemia was present in all but one case. All had a low grade fever.

Hanrahan and Miller⁵ reported the next case of this interesting syndrome eight years later. They were the first to report the beneficial effects of splenectomy in Felty's syndrome. Two years later (1934) Craven⁶ de-

scribed a case of Feltz's syndrome benefited by splenectomy. Alessandrini⁷ described a similar case the same year, but the patient refused splenectomy. Fitz⁸ reported a case in 1935.

Complete autopsy findings have been reported in two cases. In one case reported by Price and Schoenfeld⁹ in 1934, the spleen weighed 510 grams. It was soft in consistency on section. It showed diffuse fibrosis and dilata-

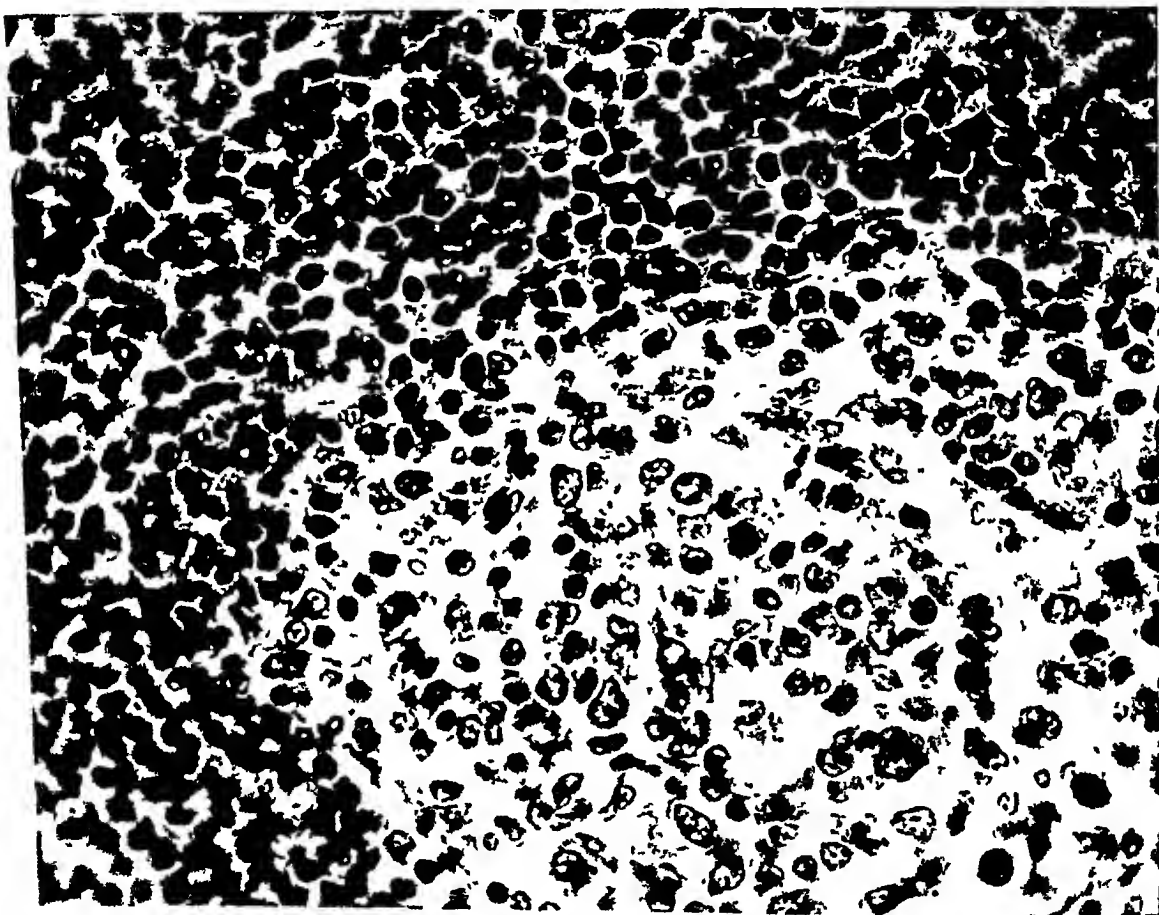


FIG. 3. Case M. Y. High power photomicrograph showing the abundance of plasma cells in the germinal center of a Malpighian body. Hematoxylin-eosin. $\times 765$.

tion of the splenic sinuses. The latter showed areas of myeloid activity with numerous plasma cells and eosinophiles. An occasional bone marrow giant cell was present. The sternal marrow showed hyperplasia with few bone marrow giant cells. Active myelosis was present throughout. In the case reported by Williams¹⁰ in 1936, the spleen weighed 260 grams. The capsule was smooth, gray and glistening. The pulp was dark red, firm, and rather relatively dry. The trabeculae and Malpighian corpuscles were not very distinct. The sternal marrow showed numerous nucleated red blood cells, some of myeloid cells and only a few granulocytes. These granulocytes were mostly myelocytes, rare polymorphonuclear leukocytes, and numerous monocytes.

Curtis and Pollard¹¹ have recently described the pathological findings in biopsy specimens of the calf muscles of four patients with atrophic arthritis associated with leukopenia, splenomegaly, anemia and adenopathy, four cases of atrophic arthritis associated with splenomegaly without leukopenia, and four cases of atrophic arthritis associated with neither splenomegaly nor leukopenia. The pathological picture was essentially the same in all, i.e., peri-

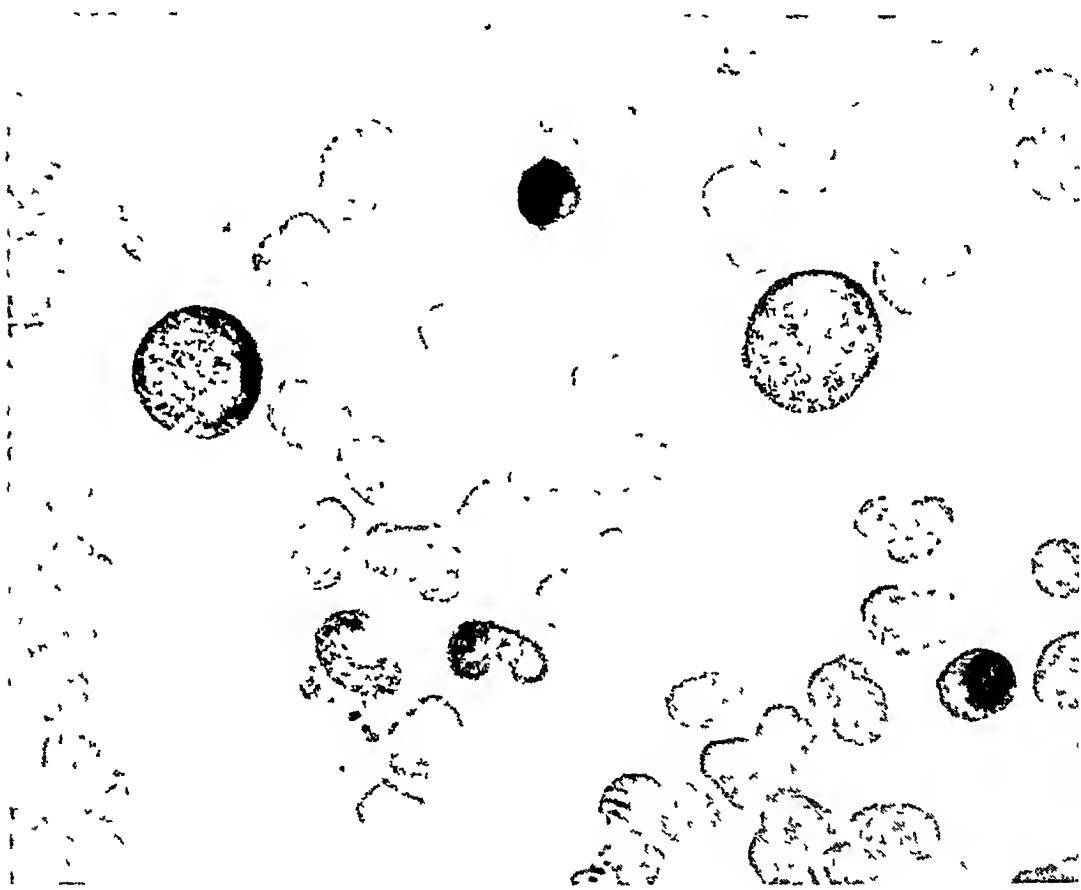


FIG 4 Case M Y Sternal marrow from a white female, aged 45, with atrophic arthritis, leukopenia, secondary anemia, splenomegaly, tachycardia and low grade fever (Felty's syndrome). This photomicrograph shows two myelocytes, one metamyelocyte and one band form. Another myelocyte was seen in the same field but is not shown on this photograph. Two normoblasts are shown. The hyperplastic nature of the marrow is further suggested by the differential given in the text of this article. Giemsa's stain $\times 900$.

vascular round cell infiltration and an increase in the interstitial nuclei. Dawson,¹² Hench,¹³ and others¹⁴ have previously stated that Felty's syndrome is a variety of atrophic arthritis.

The leukopenia and secondary anemia characteristic of Felty's syndrome is not due to bone marrow depression. Sternal marrow studies performed on two (figures 4 and 5) of the three reported cases in this paper showed a hyperplastic marrow. Marked erythropoiesis and myelopoiesis were noted. A similar type of marrow activity was shown in the case reported by Price

and Schoenfeld⁹ The writer¹⁵ has studied the bone marrow in 12 cases of typical atrophic arthritis (figure 6) All had a similar hyperplastic marrow Therefore, a hyperplastic marrow is characteristic of atrophic arthritis in general and is not typical of Felty's syndrome It probably occurs in all types of infectious disease except those cases in which the bacteria produce a bone marrow depression, as in typhoid fever, resulting in leukopenia in-

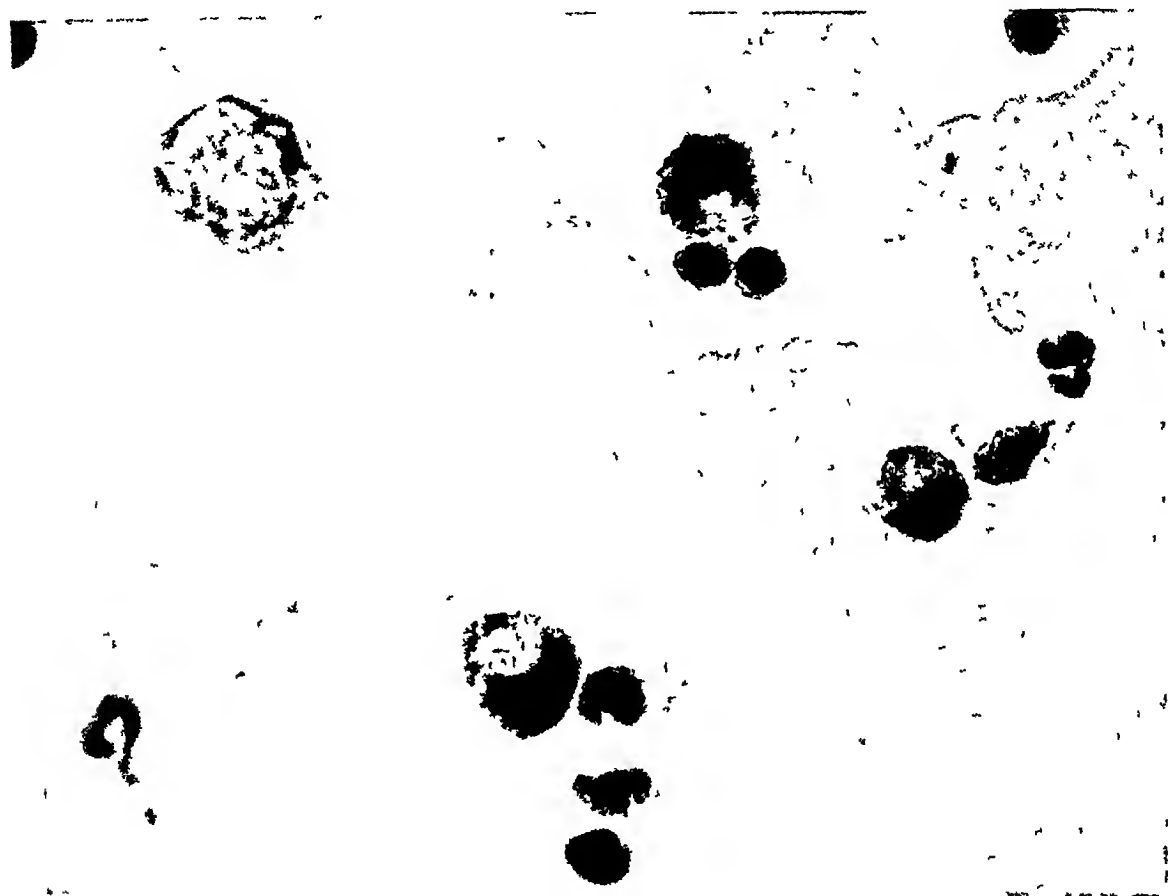


Fig. 5 Case M. B. A white female aged 49, with atrophic arthritis, leukopenia, severe anemia, splenomegaly, low grade fever and tachycardia (Felty's syndrome) This photomicrograph shows one premyelocyte, three myelocytes, one metamyelocyte, one band cell and three segmented. Three normoblasts are shown. One lymphocyte is present. The hyperplastic nature of the marrow is further suggested by the differential given in the text (from article "Weil's Arthritis," 8/5/50)

photomicrograph taken from the primary atrophic arthritis of at least a partial hyperplastic picture found in it. The differential count was as follows: myelocytes 7 per cent, eosinophils 1 per cent, metamyelocytes 16 per cent, segmented 16 per cent, lymphocytes 16 per cent, normoblasts 8 per cent, normoblasts 16

Radiographic pictures of the joints involved in Felty's syndrome are not unlike those seen in the usual type of atrophic arthritis. Decrease in the joint space, with associated articular cartilage destruction, decalcification, flexion deformities and ankylosis are demonstrated by the radiographs shown in cases M Y and M B (figures 7, 8, and 9). Felty emphasized that the cases he described showed neither widespread physical nor hemat-

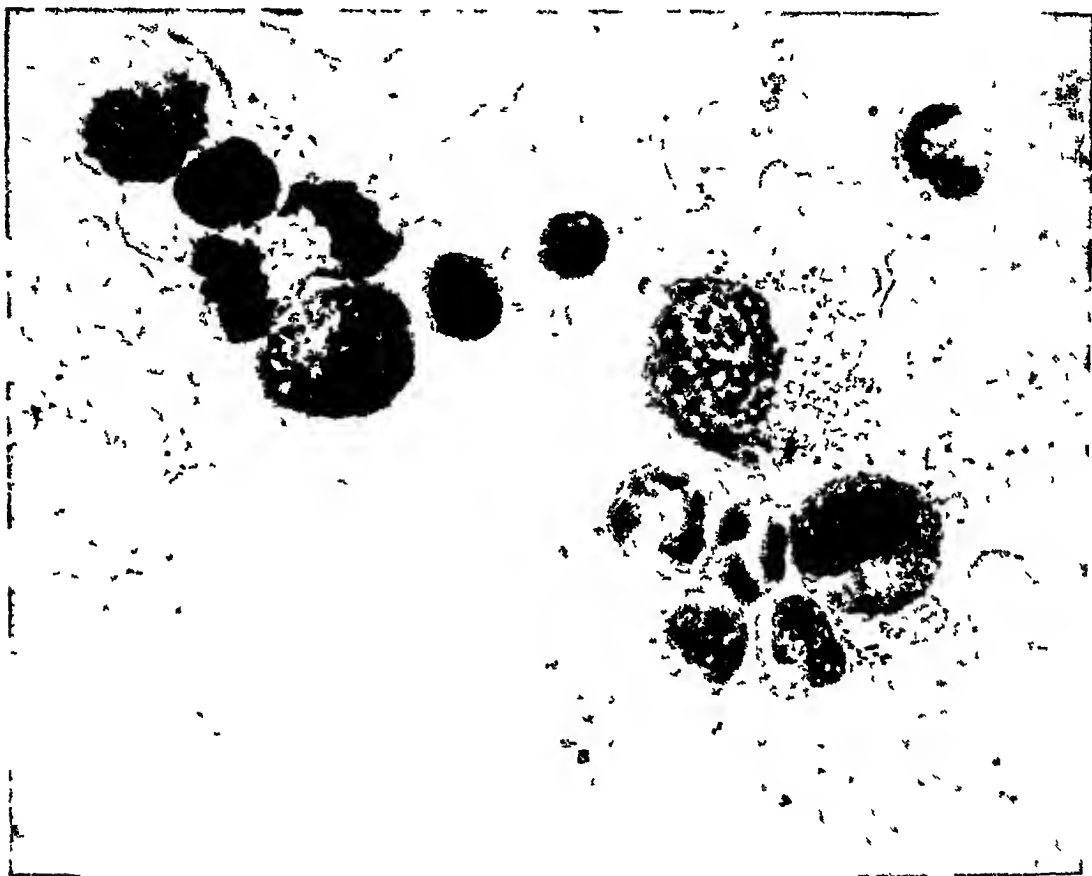


FIG 6 Case V Y Sternal marrow from a white female, aged 31, with moderately advanced atrophic arthritis (arthritis vulgaris). This photomicrograph shows one premyelocyte, three myelocytes, one metamyelocyte, two band forms and two segmented indicating hyperplasia of the myeloid series. Active myelosis is shown by karyokinetic division of a myeloblast, one late erythroblast, and one normoblast present in the same field. One lymphocyte is shown. Wright's stain. $\times 900$

genographic joint destruction. However, he spoke of a two year history of arthritis, and described only five cases. No doubt a larger series of cases and a longer period of observation would have shown cases with typical joint destruction and deformities characteristic of atrophic arthritis.

CASE REPORTS

Case M Y A 45-year-old white female was seen complaining of painful, swollen, stiff joints. The present illness began seven years previously, at which time pain, swelling and increase in local heat were noted in the left knee. Practically all

joints of the body became involved in gradual succession. Actual deformity of the finger and knee joints was first noted two years previously. She had not been able to walk for the preceding 18 months because of flexion deformity of the knee. She had had rare sore throats. Her teeth had been removed four years previously without benefit to the joints. Her father had crippling arthritis. She had been married 19 years and had two children living and well. She had lost about 40 pounds since the onset of the present illness.



FIG. 7. (Case M. Y. (Helm's syndrome). Radiographic photograph of the right knee joint showing the typical flexion deformity and narrowed joint space characteristic of atrophic arthritis. Lateral view. This picture was taken before orthopedic measures to straighten the joint were attempted.

1. The patient has a history of chronic arthritis.

flexion deformity was present in both elbows. Increase in local heat was present in both these joints. Pain on motion and complete lack of abduction were present in both shoulders. There was no motion in either knee, and both knees had a right angle deformity. Swelling and increased local heat were present in both these joints. There was practically no motion in the ankles. The anterior arches were flat.

The laboratory examination was of unusual interest due to the persistent leukopenia which responded to no method of therapy except persistent blood transfusions.

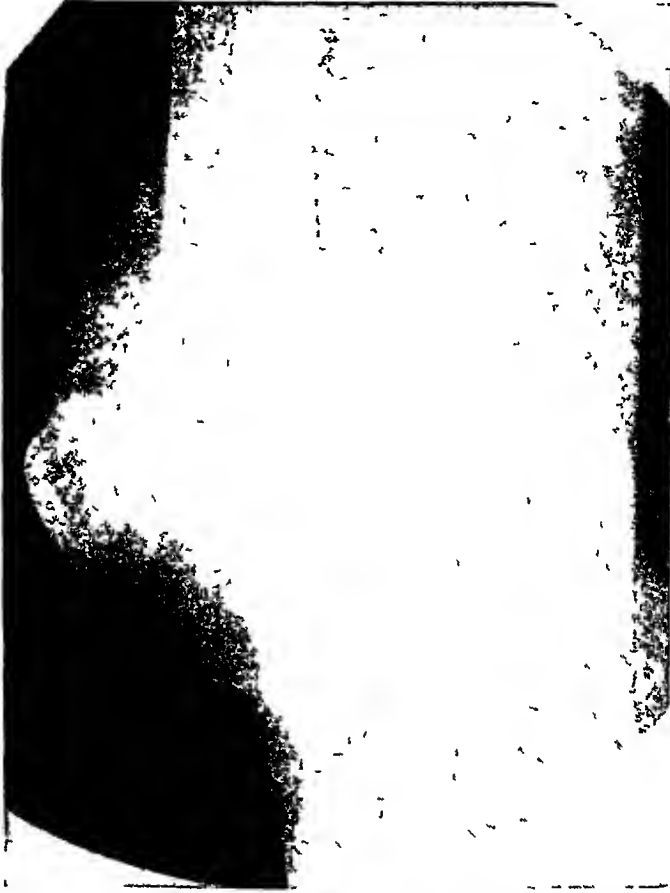


FIG 8 Case M Y (Felty's syndrome) Radiographic photograph of the right knee after it was straightened by plaster application. The general health improvement that followed splenectomy permitted this procedure to be carried out. Some subluxation is present.

The blood transfusions acted as temporary agents in raising the white blood count and improving the secondary anemia. Reduced iron, liver, and yellow bone marrow all resulted in no improvement. Figure 10 reveals the effect of all these various agents on the white blood count, red blood cells, hemoglobin and platelets. Wassermann and complement fixation tests for the gonococcus were negative. The blood uric acid was 2.80 mg per 100 cc of blood. Icterus index was 5. The reticulocyte count varied from 0.1 per cent to 7.1 per cent. Serum calcium was 9 mg, and serum phosphorus was 4.1 mg. Sternal bone marrow revealed the following interesting blood picture: 7 per cent myeloblasts, 9 per cent premyelocytes, 18 per cent neutrophilic myelocytes, 1 per cent eosinophilic myelocytes, 1 per cent basophilic myelocytes, 7 per cent metamyelocytes, 8 per cent band forms, 12 per cent segmented, 1 per cent eosinophilic segmented, 8 per cent large lymphocytes, 6 per cent small lymphocytes,

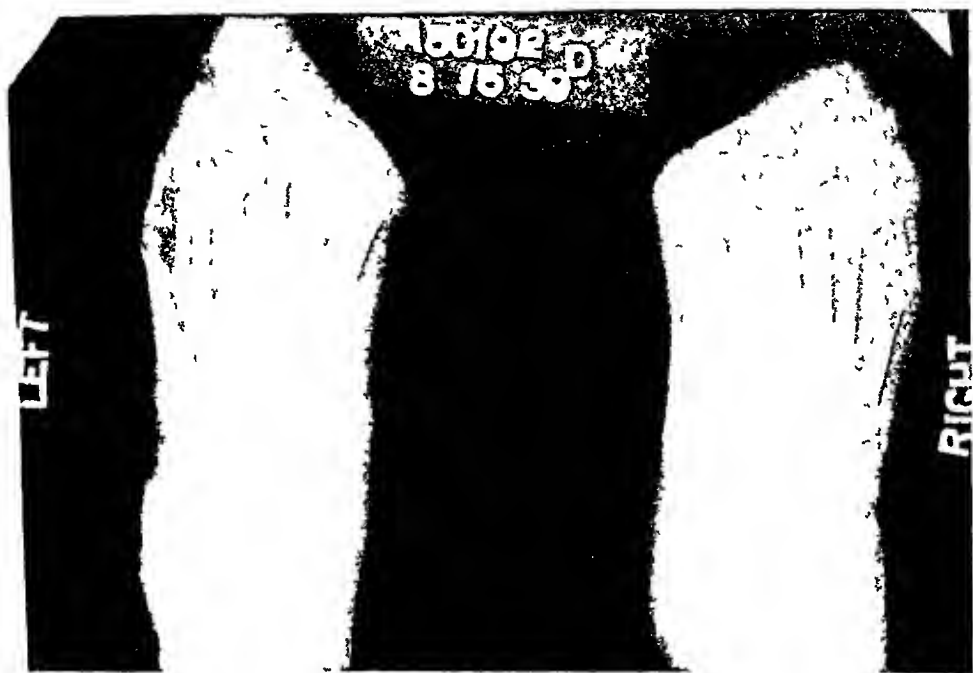
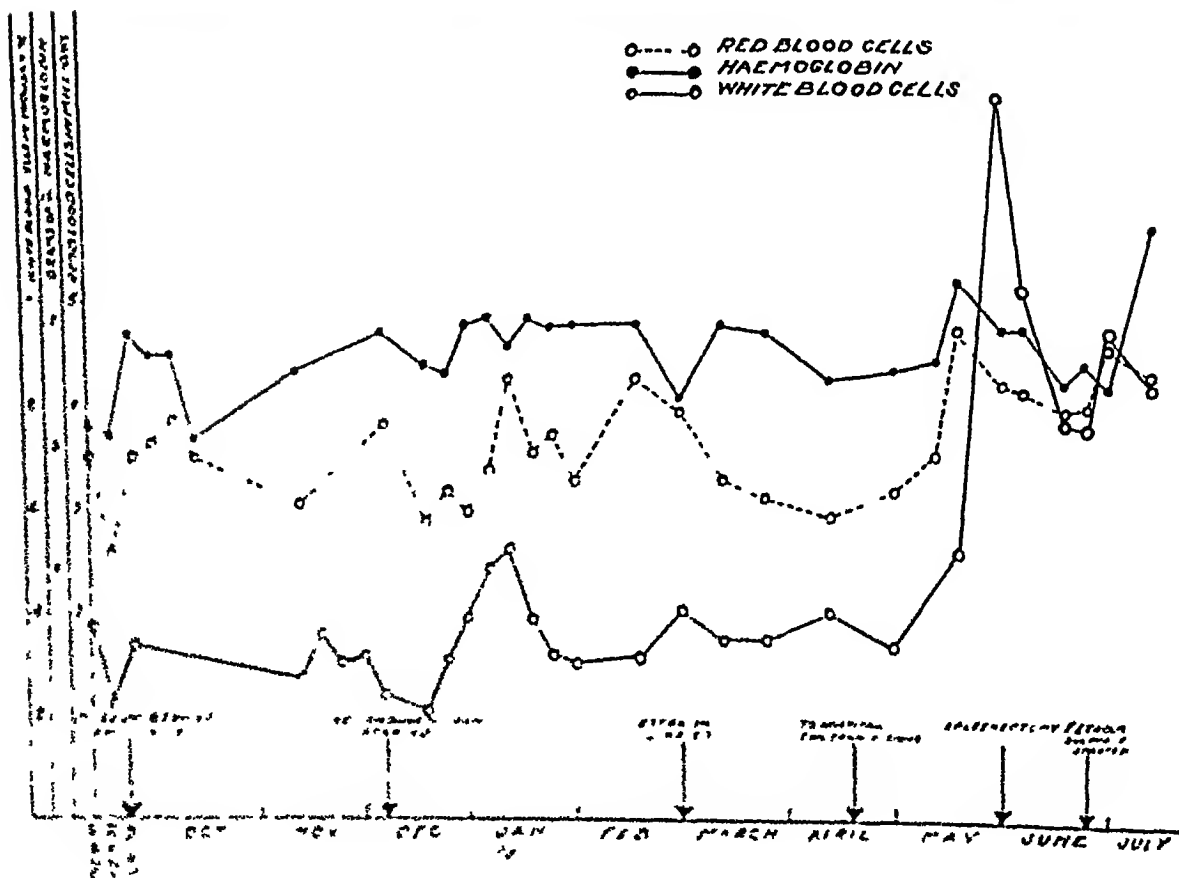


FIG. 9 Case M. B. (Telford's syndrome) Radiographic photographs of the feet showing the typical joint destruction characteristic of advanced atrophic arthritis



3 per cent megaloblasts, 9 per cent erythroblasts, 2 per cent monocytes, 2 per cent plasma cells

Since the bone marrow was found to be able to produce its cells in abundant quantities, it seemed plausible that the spleen might act as a barrier in not permitting the peripheral blood to receive these cells in sufficient quantities. A splenectomy seemed to be a rational procedure. The marked and continued improvement in the blood picture resulting from the splenectomy is shown in figure 10.

The histologic picture of the removed spleen is shown in figures 1 and 2. The Malpighian bodies were quite large and showed large germinal centers. The latter exhibited an abundance of plasma cells. The pathologist unfortunately failed to give a gross description of the spleen. The surgeon who removed the spleen stated that it was about three times normal size (14 by 9 by 4.5 cm).

No noticeable improvement in the arthritis occurred as a direct result of the splenectomy. However, the general clinical improvement permitted orthopedic measures to be carried out successfully. The radiographic photographs (figure 7) showed the flexion deformity present before the plaster casts were applied, and the radiographic picture (figure 8) showed the end result of such procedure. The patient had about 10° motion in both knees, they were straight, but there was some subluxation of the joints present. Her fever had disappeared, but a tachycardia of 100 to 110 continued. She had gained in weight, appetite, and strength.

Liver extract and yellow bone marrow failed to improve the peripheral blood picture. After all these methods failed a study of the sternal bone marrow was made. It showed a hyperplastic bone marrow as follows:

Myeloblasts	7
Premyelocytes	9
Myelocyte neutrophils	8
Myelocyte eosinophiles	1
Myelocyte basophiles	1
Juveniles	7
Band forms	8
Segmented neutrophils	12
Segmented eosinophiles	1
Large lymphocytes	8
Small lymphocytes	6
Megaloblasts	3
Erythroblasts	9
Monocytes	2
Plasma cells	2

With such evidence that the bone marrow was not aplastic and could deliver cells, why did all recognized methods of therapy fail to secure improvement of the peripheral blood? Where was the barrier between the hemopoietic centers and the peripheral blood? Was the spleen acting as a barrier? The latter conclusion seemed plausible. Splenectomy was carried out after bringing the blood up nearly to a normal level with transfusions. There was decided improvement of the patient's blood and general condition immediately following splenectomy. However, within a period of three weeks after the splenectomy, a gradual decline was observed in the blood picture and in the patient's general condition. Anorexia was a most difficult symptom to combat. The patient developed a peculiar depressed mental attitude. Frequent cheerful conversations and the forcing of highly nutritious foods rich in vitamins overcame this condition.

The above decline in the patient's condition associated with marked anorexia calls for a careful restudy of the previously reported cases showing improvement after splenectomy.

The follow-up on the two cases of Felty's syndrome^{5,6} reveals that both cases died a comparatively short time after operation. Craven's⁶ case died 14 months after operation of general inanition and a terminal bronchopneumonia. Hanrahan and Miller's⁵ case died 18 months after operation. The cause of death was not given. Both of these end results were reported by Fitz.⁸ The case reported in this paper also showed signs of general inanition resulting from her marked anorexia. However, she maintained a normal white blood count and the secondary anemia responded to iron therapy. The low grade fever disappeared following operation. No method of therapy had secured these results before operation.

Case G P A 39-year-old white female complained of painful swollen joints. The illness began 24 years previously, with painful swelling of both wrists, both ankles and of all proximal interphalangeal joints. An acute exacerbation of the arthritis occurred four years later. The patient has remained essentially unchanged since this last flareup. She had had scarlet fever at eight years of age, and had had only an occasional sore throat. She had had herpes at 20. Her Wassermann reaction was negative in 1932 but four plus in 1934. Her father had deforming arthritis. She had three children living and well. Her husband and all children had negative serological tests for syphilis.

The physical examination showed a well developed, well nourished, intelligent white female whose nude weight was 132 lbs, temperature 97.6° F, pulse rate 100 per minute, and blood pressure 130 mm Hg systolic and 96 mm diastolic. Examination of the head was negative. The teeth and tonsils had been removed. Cervical and inguinal adenopathy was present. Examination of the lungs and heart was negative. Abdominal examination revealed an enlarged, non-tender, firm spleen which was felt two fingers' breadth below the costal margin. Rectal and vaginal examinations were negative. There was fusiform swelling of the proximal interphalangeal joints characteristic of atrophic arthritis. The capsules of both knees and both ankle joints were moderately thickened. Increase in local heat and tenderness was present over the left shoulder joint. No deformities were present.

tionship between the syphilis and the blood picture. The atrophic arthritis, tachycardia, splenomegaly, leukopenia, secondary anemia, and lymphadenopathy are consistent with a diagnosis of Felty's syndrome.

Course. The arthritis entirely subsided under treatment with hemolytic streptococcal vaccine. She was given nine capsules of extralin daily beginning March 1, 1940, with slight improvement of the leukopenia.

Case M B (3) A 49-year-old white female was seen complaining of painful swollen joints. The present illness had begun 10 years previously at which time pain

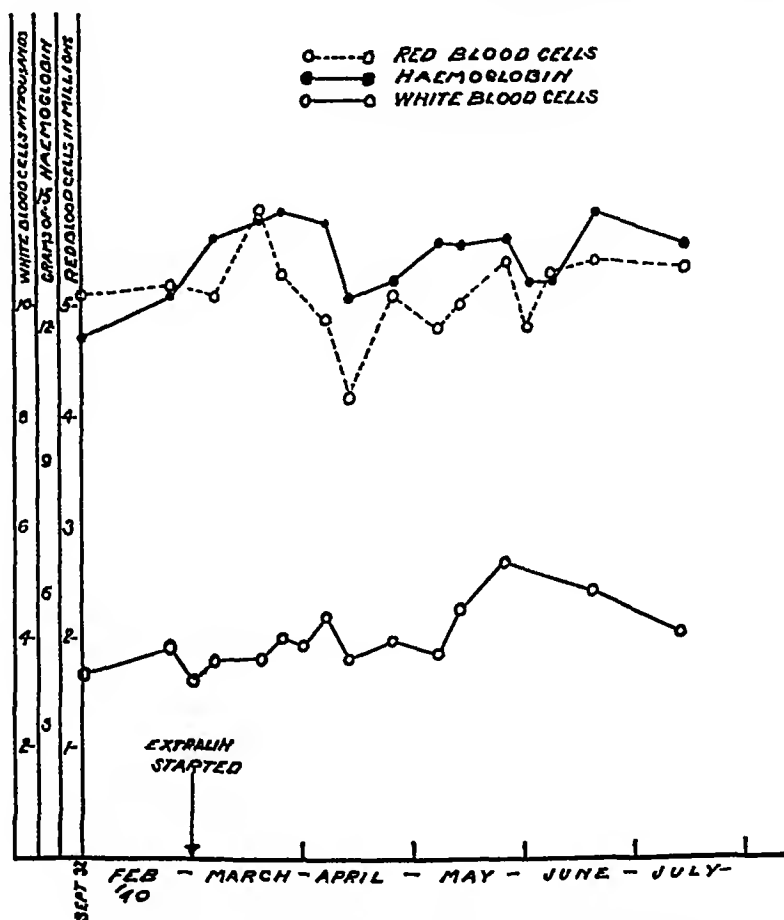
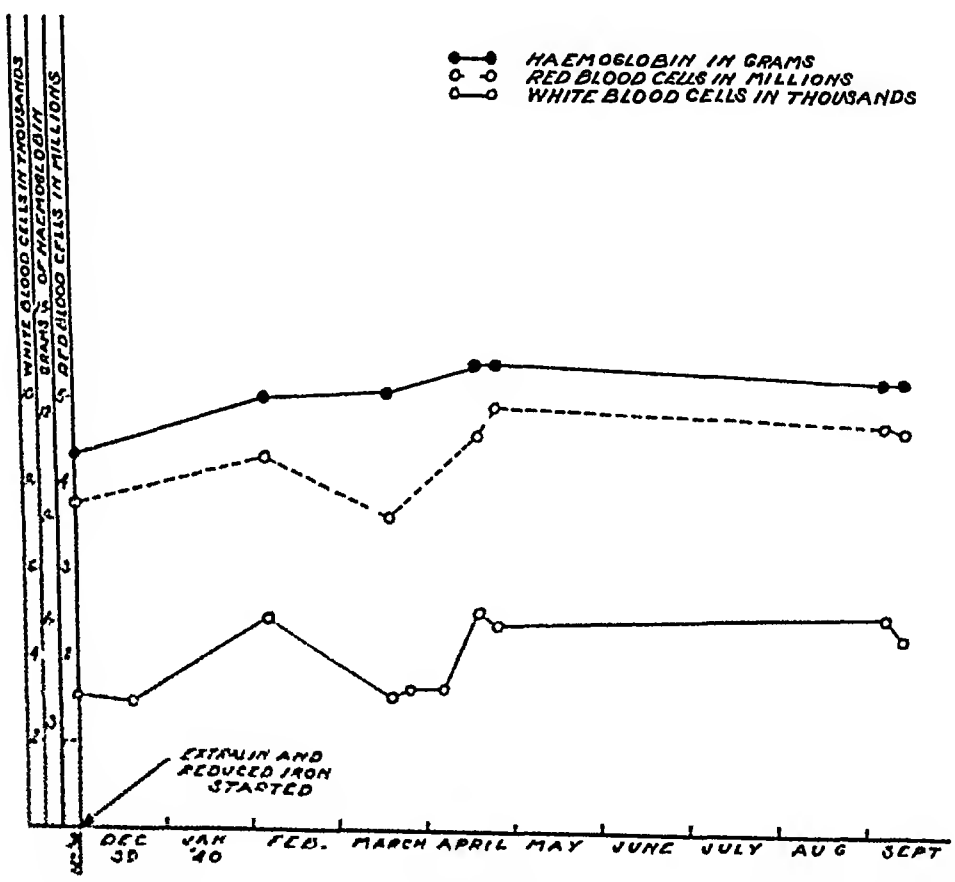


FIG 11 Case G P Effect of extralin on blood regeneration

was noted in the balls of the feet upon walking. Swelling was later noted in this area. The knees, all the finger joints, wrists, elbows and ankles have progressively become swollen, painful and warm to the touch. Marked pain on motion soon became evident in the shoulders and hips. The joints had been made much worse by two exacerbations, one of which had occurred seven years previously and another three years previously. The latter exacerbation was preceded by erysipelas. She had lost considerably in weight since the onset of the arthritis. The exact amount was unknown.

The physical examination revealed an undernourished white female lying more or less helpless in bed with typical deformities of the joints characteristic of advanced atrophic arthritis. Temperature was 99° F, pulse rate 86 per minute, blood pressure 124 mm Hg systolic and 70 mm diastolic. The pupils reacted to light and accommodation. All the teeth were out. The tonsils were small and appeared innocent.

Examination of the neck, lungs and heart was negative The spleen was barely palpable It was firm and nontender The finger joints were deformed in the most grotesque manner Most of the phalanges dangled from their joints Flexion deformity was present at the metacarpophalangeal and wrist joints Ulnar deviation was marked The elbows were fixed in flexion Marked abduction deformity of the shoulders was present The hips were in flexion deformity with only about 20° motion present, 30° flexion deformity was present in both knees There was slight shortening of the Achilles tendon of both heels No increased local heat or marked



12 Case M B Effect of extralin and iron on blood regeneration

Sternal marrow showed a hyperplastic picture (figure 5) The differential count was as follows Neutrophilic myelocytes 10 per cent, eosinophilic myelocytes 5 per cent, metamyelocytes 7 per cent, band forms 10 per cent, segmented 18 per cent, lymphocytes 20 per cent, eosinophilic segmented 5 per cent, megaloblasts 4 per cent, erythroblasts 4 per cent normoblasts 17 per cent

In the therapy of this interesting syndrome, one should first remember that the disease is a chronic constitutional one with all the signs and symptoms of chronic infection Its general management should be no different from that of tuberculosis Absolute bed rest, a highly nourishing diet rich in vitamins, and mental as well as physical relaxation are required A careful study of the peripheral blood should be made on several occasions to rule out aleukemic leukemia and aplastic anemia A careful history for undulant fever, agglutination tests, blood cultures and skin tests should rule out *Brucella abortus* infections Tuberculosis must be ruled out The arthritis per se rules out Banti's disease Most important, bone marrow studies should be done to determine the degree of activity or inactivity of the marrow If inactivity is present splenectomy could not possibly be of value Bone marrow stimulants such as liver, yellow bone marrow, pentnucleotide, etc, should be tried If the marrow is hyperplastic and all other known methods have failed, splenectomy is in order

Three cases of atrophic arthritis associated with a syndrome described by Felty are presented The leukopenia and secondary anemia were successfully controlled in two cases by giving liver extract or liver extract and iron All efforts to improve the peripheral blood picture failed in one case Splenectomy proved of value in this latter case Bone marrow studies in two of these patients revealed a hyperplastic marrow The deficiency of cells in the circulating blood seems not to depend upon inadequate formation by the marrow, but upon some barrier to their entrance into the circulation The most probable barrier is the spleen as demonstrated by the improvement noticed in the case reported in this paper and the cases previously reported in the literature

Splenectomy should be done only after all conservative measures fail One patient reported in this paper had a leukopenia for eight years without apparent ill effect Her blood picture either improved spontaneously or else the liver extract was effective therapeutically Improvement in the blood picture after splenectomy has been associated with general clinical improvement It has not directly altered the course of the arthritis

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PROSTATITIS—A CAUSE OF ACUTE OR RECURRENT ABDOMINAL PAIN^{*}

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ABDOMINAL pain, when acute, is a symptom which frequently presents a baffling diagnostic problem. If the pain is chronic, this problem often becomes even more perplexing. In a series of six patients coming under my observation, each presenting abdominal pain as his major complaint, the usual causes for such pain were not apparently operative in any case. However, a thorough physical examination showed each to have an inflammatory process residing in the prostate. This finding was confirmed by the presence of definite pus in the expressed secretions of the gland, and, in each instance, no other objective findings were noted which were considered as relevant to the chief complaint. Before conclusively inculcating the prostate as a source for the subjective sensation of pain in the abdomen, I shall outline briefly the history and clinical course of these patients.

CASE REPORTS

Case 1 A white male, aged 25, unmarried, was first examined in July 1936. His chief complaint was pain in the right lower quadrant of the abdomen of four months' duration. Associated symptoms included a continuous burning sensation at the tip of the penis for two weeks and occasional fleeting pains in the rectum and coccygeal region for many months. Previous observation and examination indicated the probable diagnosis was either a strain of the abdominal musculature, or chronic appendicitis. The patient was advised to wear an abdominal supporting belt which he did for two months with no relief. The patient denied venereal disease by name and symptom. He had had no previous sexual experience but admitted to frequent masturbation over a period of years. Physical examination disclosed normal heart and lungs. Palpation of the abdomen disclosed no spasticity or tenderness and no masses or enlarged organs. Examination of the prostate showed it to be slightly enlarged and boggy and to be distinctly tender especially in the right lateral lobe. When pressure was exerted over this more tender area the patient experienced abdominal pain identical in character and location to that felt subjectively. Microscopic examination of the prostatic smear showed many large clumps of pus cells. No gonococci were found. Local treatment including massage, diathermy, and instillations of silver nitrate solution into the posterior urethra effected complete relief from all symptoms. A recent examination of the patient, two years after treatment, showed him to be free from all signs and symptoms previously noted.

Case 2 A white male, aged 70, complained of constantly recurring and frequently severe pain in the right lower quadrant of the abdomen, which occasionally radiated to the left lower quadrant. This pain had begun to trouble him 10 years prior to this examination, and was constantly increasing in frequency and severity. Within the last three years symptoms of prostatic obstruction also began to appear. These included slowing of the stream, difficulty in starting the flow, dribbling, etc. Within the past two years, he began to experience angina pectoris and symptoms indi-

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cative of cardiac insufficiency. When the pain had first presented itself, the patient was advised that a hernioplasty for the cure of a longstanding hernia might effect relief of his abdominal pain. The operation was done, but it failed to accomplish this result. Three years afterward a hemorrhoidectomy was performed on the assumption that the hemorrhoids and concomitant constipation might be the responsible factor. Physical examination showed an elderly white male appearing chronically ill. Lungs were emphysematous, and contained bibasal râles. The heart was considerably enlarged, especially to the left. The heart sounds were forceful with a long blowing systolic murmur present at the apex. Blood pressure was 210 mm Hg systolic and 140 mm diastolic. The liver was enlarged to two fingers' breadth below the costal margin and had a smooth tender edge. The prostate was distinctly enlarged and contained many nodules. It was very tender, especially in the right lateral lobe, and pressure over this area elicited exactly the same type of pain complained of by the patient. These findings were entirely corroborated by a competent urologist, Dr. Perry Katzen of Brooklyn, whom I asked to confirm my own observations. Prostatectomy was subsequently performed but the cardiac status was so poor that the patient did not survive the procedure.

Case 3 A white male of 23 presented himself in March 1938 complaining of severe pain in the right lower quadrant of the abdomen associated with vomiting and fever of one day's duration. Associated symptoms included burning and frequency of urination. He admitted illicit sexual contact two days prior to the onset of his illness. He had no previous illness of consequence except for an untreated gonococcal urethritis at 19. Physical examination revealed the patient to be acutely ill. Temperature was 101° F, the pulse rate 100 per minute. The throat, heart and lungs were negative. There was marked tenderness in the right lower quadrant and suprapubic region, with considerable muscle spasm of involuntary nature. Rectal examination showed no tenderness in the region of the appendix or either iliac fossa. The prostate was moderately swollen and exquisitely tender. A smear of the gently expressed secretions of the gland contained pus and many gram-negative intracellular diplococci. The following day a fully developed urethritis was present.

Cases 4, 5, and 6 I have grouped the accounts of these cases because each exhibited strikingly similar histories and physical findings. Ages were 39, 31, and 25 respectively. All were married and as a rule practiced coitus interruptus. Cases 4 and 5 admitted also a previous gonococcal infection. The major presenting complaint in each was chronic recurrent pain in the abdomen. In cases 5 and 6 a probable diagnosis of chronic appendicitis had been made and operation recommended. All showed a tender prostate, and the presence of infection was confirmed by laboratory examination. Conservative local therapy directed toward the prostate achieved relief of signs and symptoms.

ANALYSIS OF CASES

This series of patients all presented a number of symptoms and signs which constitute a fairly definite clinical syndrome. All complained of abdominal pain, principally of a chronic variety, and most frequently located in the right lower quadrant. In each instance, also, the prostate was tender on palpation. Expressed prostatic secretions uniformly showed pus. When the patient first-presented himself the complaint of pain had been present in all but one case for from one to 10 years. In three cases the diagnosis of chronic appendicitis had been seriously entertained. Case 2 was subjected first to a hernioplasty and subsequently to a hemorrhoidectomy, primarily for relief of the pain in the abdomen, but no relief of the presenting symp-

tom was achieved. Case 3 showed enough objective findings to indicate strongly the necessity for a possible appendectomy. The etiologic factor determining the production of the prostatitis varied, being masturbation in case 1, prostatic hypertrophy and infection in case 2, a recurrent gonococcal urethritis in case 3, and coitus interruptus in the remainder. Masturbation and coitus interruptus have for some time been recognized as potent causative agents in the development of chronic prostatitis. Dr Hugh Young, in Nelson's Loose-leaf Surgery, inculcates masturbation as such an etiologic agent. It is most significant and worthy of emphasis that pressure over the tender portion of the prostate reproduced exactly the pain complained of by the patient. This finding led me to the natural conclusion that prostatic disease could simulate chronic painful intra-abdominal disease. I was prompted, therefore, to confirm my findings by consultation with a competent urologist. This I did as stated above in the history of case 2. Dr Katzen stated at the time that he had no previous knowledge of the existence of any relationship between pain in the abdomen and prostatic disease. It is not difficult to understand why such cases do not as a rule come under the care of the urologist. The major complaint being abdominal pain, the patient would naturally present himself first to his family physician or to a surgeon or gastroenterologist. Since a relationship between abdominal pain and prostatic disease has not been particularly stressed in the past, it is possible that the prostate as an offending agent may be occasionally overlooked.

COMMENT

Ever since the work of Head, whose brilliant investigations in the field of subjective pain sensation have led to a better fundamental understanding of the problem, we have become more and more accustomed to the idea that "Pain is not where you find it." The theories formulated by Head, relating to the vagaries and habits of the human nervous system in appreciating painful sensations, have uncovered a whole new approach to the diagnosis and treatment of organic disease. A careful perusal of the more recent texts on the subject of urology failed in most cases to reveal any mention of the relationship between abdominal pain and prostatic disease which I have here tried to establish. Only Wesson¹ has directly mentioned such a relationship, and even he emphasized the seminal vesicles rather than the prostate as the source of pain. However, it is obvious that with a common innervation for both structures it would be possible to assume the prostate at fault occasionally as well as the seminal vesicles. It is common knowledge that disease in the prostate may produce pain in the small of the back, the buttocks, the thighs, the scrotum, the groins, and even the leg or foot. Unfortunately, the exact innervation of the prostate and other parts of the lower genito-urinary tract is not as yet known, but it is believed that the pelvic nerve provides the most important pathway for both afferent and efferent impulses for this entire region, including the bladder, seminal vesicles, prostate and

urethra With the knowledge gained from the many studies of referred pain it is not difficult to understand how pain impulses might readily be referred over sensory pathways at higher levels in the cord, than might be anticipated, so that a relatively wide range of abdominal surface areas might conceivably be affected. A similar type pain in unusual or unexpected areas is met with in the case of disease of other organs. As Libman in particular has pointed out, this is true of pain of cardiac origin. The pain of angina and coronary spasm not uncommonly radiates to such regions as the teeth, ear and leg. Suffice it, therefore, again to emphasize the vagaries of pain in the abdomen, and to suggest that when a cause for such pain is not obvious in the male patient a thorough examination of the prostate be included.

SUMMARY

1 A group of cases is presented exhibiting abdominal pain in which a diseased prostate was found to be the source of such pain.

2 A plea is made for the examination of the prostate in all male patients, especially in those exhibiting abdominal pain as a symptom.

3 It is suggested that suspected but not proved cases of chronic appendicitis in males be investigated as possible cases of chronic prostatitis to determine whether or not such disease might possibly be masquerading as appendicitis.

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EOSINOPHILIA IN FATAL ASTHMA; STUDIES OF BONE MARROW AND MYOCARDIUM *

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THE finding of marked eosinophilic infiltration in the bone marrow and heart of a man who had suddenly died in an asthmatic paroxysm stimulated us to review the literature and previous autopsies on cases of asthma at the Rhode Island Hospital in order to obtain more information relative to this condition

The literature lists few autopsied cases Coca¹ in 1931 summarized them and found 33 for his discussion Lamson and Butt² in 1937 brought the series up to date, finding 50 cases and adding 48 of their own Fowler³ in that same year reported two cases, and Thieme and Sheldon⁴ in 1938 reported seven in which death could be attributed to the asthmatic paroxysm We have reviewed all of these reports

In addition, the autopsy records of the Rhode Island Hospital from January 1, 1929 to February 8, 1940 were searched for cases of fatal asthma Of 3,241 autopsies performed during those years, we are reporting six in which there was a definite asthmatic history Bone marrow from the upper third of the shaft of the humerus and from the lumbar vertebra was available for study in four of the six cases One autopsy is deficient in material for extensive study, but is included because of the cardiac pathologic lesions found

Only the pertinent material will be given, and the case which led us to make this study will be presented first

CASE REPORTS

Case 1 W W , white male, aged 27, was admitted February 2, 1940

History The family history revealed twin cousins with asthma⁵ The past history was irrelevant except for an attack of rheumatic fever four years previously, at which time he had spent two months in bed He had had a tonsillectomy in childhood He had always been prone to obesity and had always some shortness of breath attributed to it About the age of seven he had his first attack of wheezing According to his family physician, no other attacks occurred until November 1939 at the age of 27 A chronic nasal obstruction was relieved in January 1939 by the removal of several nasal polyps Roentgenograms in May 1939 revealed ethmoidal disease, and these sinuses were curetted in July of that year Asthma, according to the patient, really began in October 1939 The attacks were mild at first, gradually increasing in duration and severity For the fortnight before entry attacks were continuous, with medication giving only transient relief No causative factors could

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be determined. Skin tests in January 1940 showed questionable reactions only to rice, timothy and cotton seed.

Physical Examination: On the day of admission the temperature was 97.6° F., the pulse 132, respirations 35, and the blood pressure 115 mm. Hg systolic and 60 mm. diastolic. The patient was an obese white male weighing 240 pounds, sitting up in

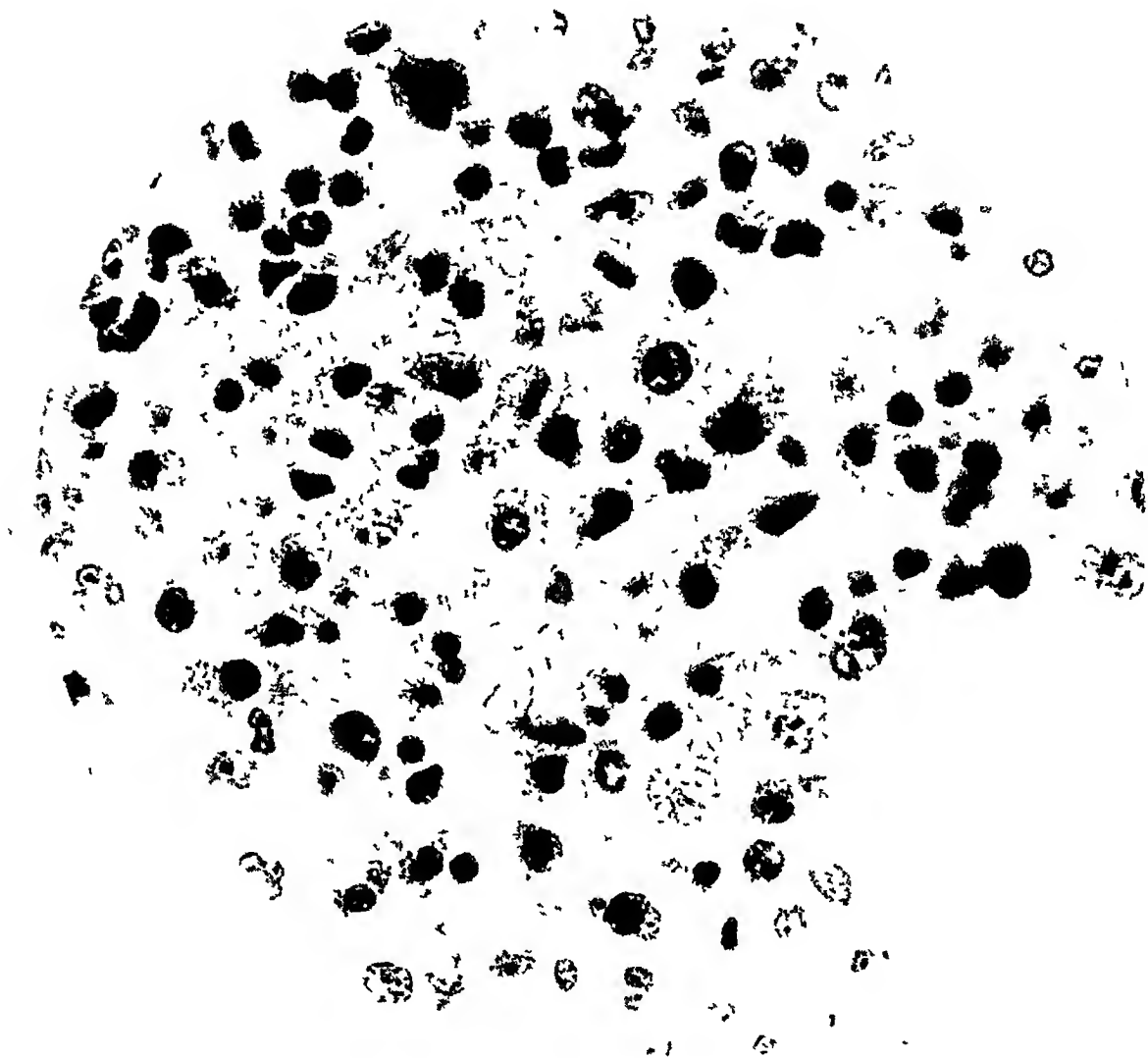


FIG 1 Bone marrow, showing many eosinophilic polymorphonuclear leukocytes

bed with mild respiratory difficulty. No cyanosis was noted. The nose was partially blocked. The heart was not enlarged to percussion. The sounds were distant with no audible murmurs. Characteristic asthmatic râles were heard throughout both lung fields.

Laboratory Findings Roentgenogram of the chest on February 3 showed mottling irregularly scattered through both sides suggestive of bronchopneumonic consolidation. Electrocardiogram showed a rate of 104 with normal conduction time. There was a small S-wave in Lead I, a deep S in Leads II and III, and the T-waves were not remarkable. The S-T segment was deep and a definite left axis deviation was noted.

The record was interpreted as being abnormal but significant of no special type of heart disease. The urine and Wassermann reaction were negative. The white blood count was 8100. The differential count showed neutrophilic leukocytes 66 per cent, lymphocytes 20 per cent, and eosinophilic leukocytes 14 per cent. The blood urea nitrogen was 6.3 mg per cent and the blood glucose 74 mg per cent.

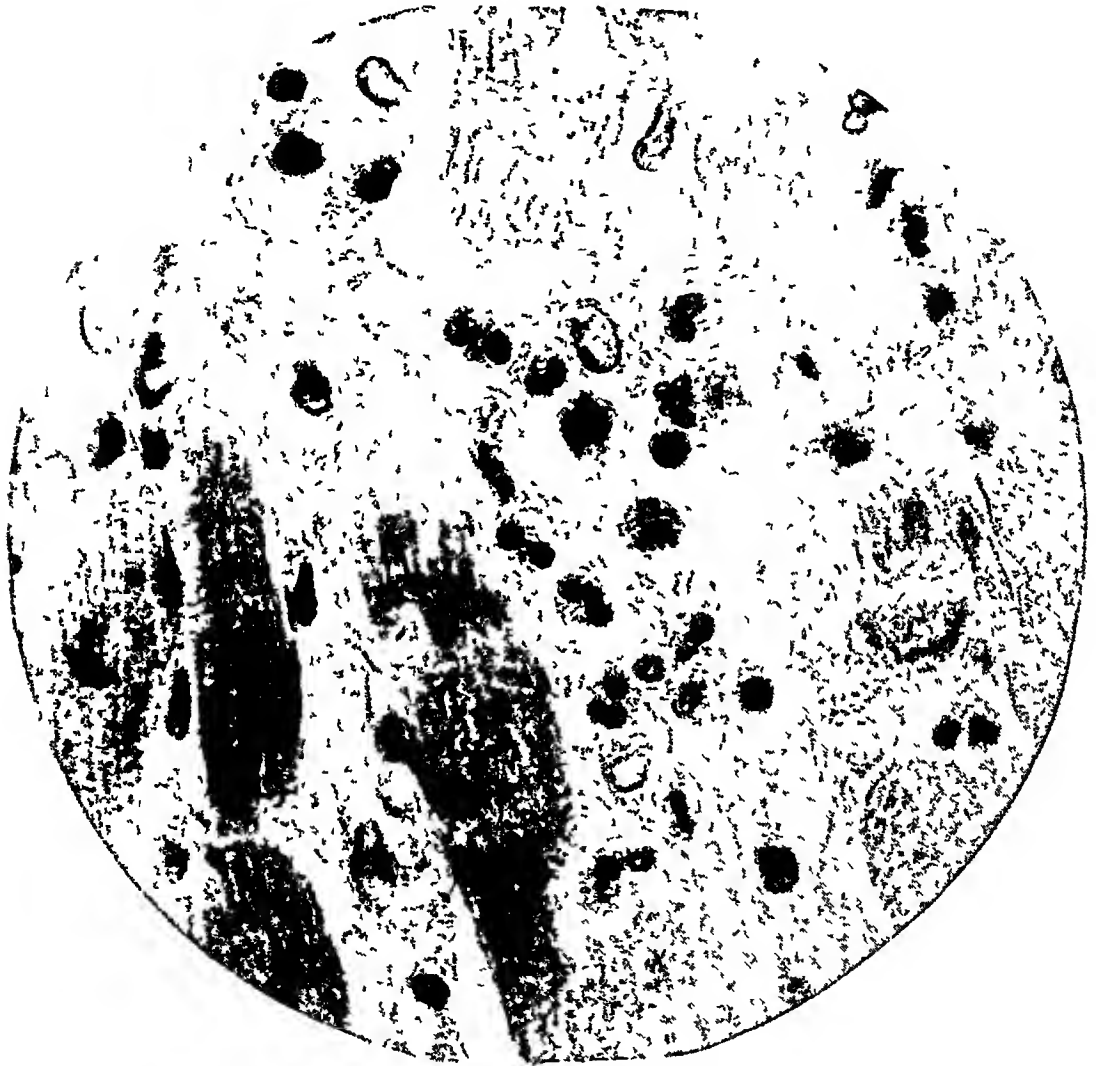


FIG 2 Myocardium showing infiltration of the intermuscular spaces by eosinophilic polymorphonuclear leukocytes

Course Under adrenalin-in-oil there was slight improvement until the sixth hospital day. That morning a severe attack commenced. The usual therapy of aminophyllin, adrenalin, and oxygen gave no improvement. During that night, his temperature being 99.8 F, and pulse 180, he was given paraldehyde and other sedatives with no effect. Pantopon, gr $\frac{1}{4}$, administered early in the morning six hours after the last preceding medication, resulted in the first sign of improvement. He was found dead in bed two hours later.

Postmortem Examination Adiposity was especially prominent about the shoulder and pelvic girdles.

The heart weighed 450 gm. The wall of the right ventricle averaged 15 mm. in thickness, the wall of the left ventricle 10 mm. There were no changes in the coronary arteries. It was in the histological examination of the myocardium that most interesting findings were revealed. The myocardial fibers in many areas had lost their striations and in places had assumed a pinkish homogeneous stain. In many of these

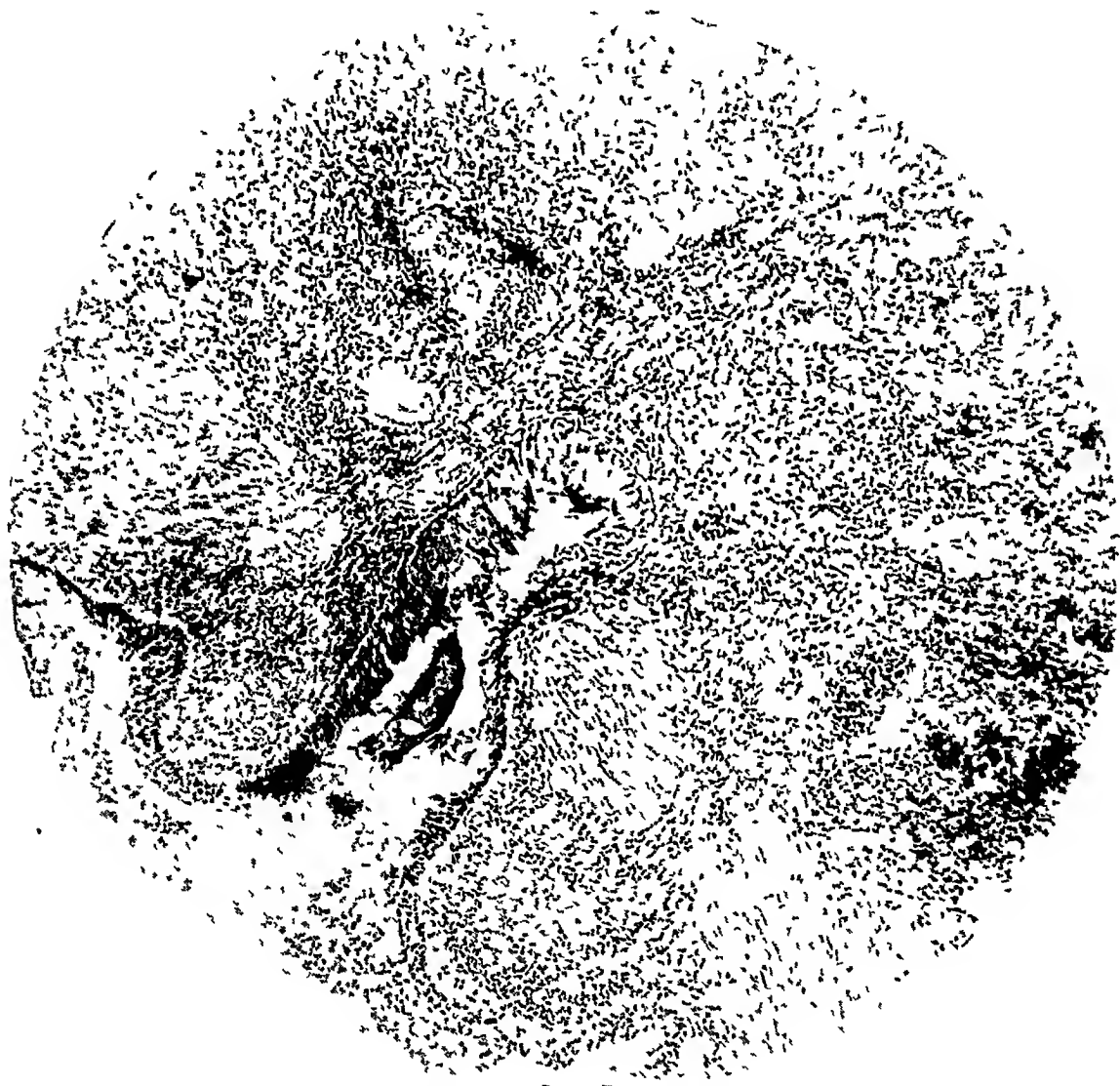


FIG 3 Bronchus showing squamous metaplasia of lining epithelium, thickened basement membrane, chronic bronchitis, smooth muscle, and a few mucous glands

areas of degeneration there was a massive infiltration of eosinophilic polymorphonuclear leukocytes with only a few lymphocytes and plasma cells. The eosinophilic polymorphonuclear leukocytes were not limited in distribution to areas of necrosis, but were also evident in the intermuscular and perivascular spaces, as well as the subepicardial fat. Deposits of fibrin were occasionally found in some of the intermuscular spaces. No actual fibrosis was present. In a few instances near small blood vessels and in the intermuscular spaces there were small foci of necrosis about which were collections of lymphocytes, plasma cells, and large mononuclear cells. There were

no eosinophilic polymorphonuclear leukocytes in these accumulations, nor were any giant cells seen. Very occasionally the myocardial nuclei were found to be swollen and vacuolated (figure 2).

The right lung weighed 650 gm and the left 450 gm. The lungs were light and floated in water. Upon section numerous bullous air pockets collapsed. The walls

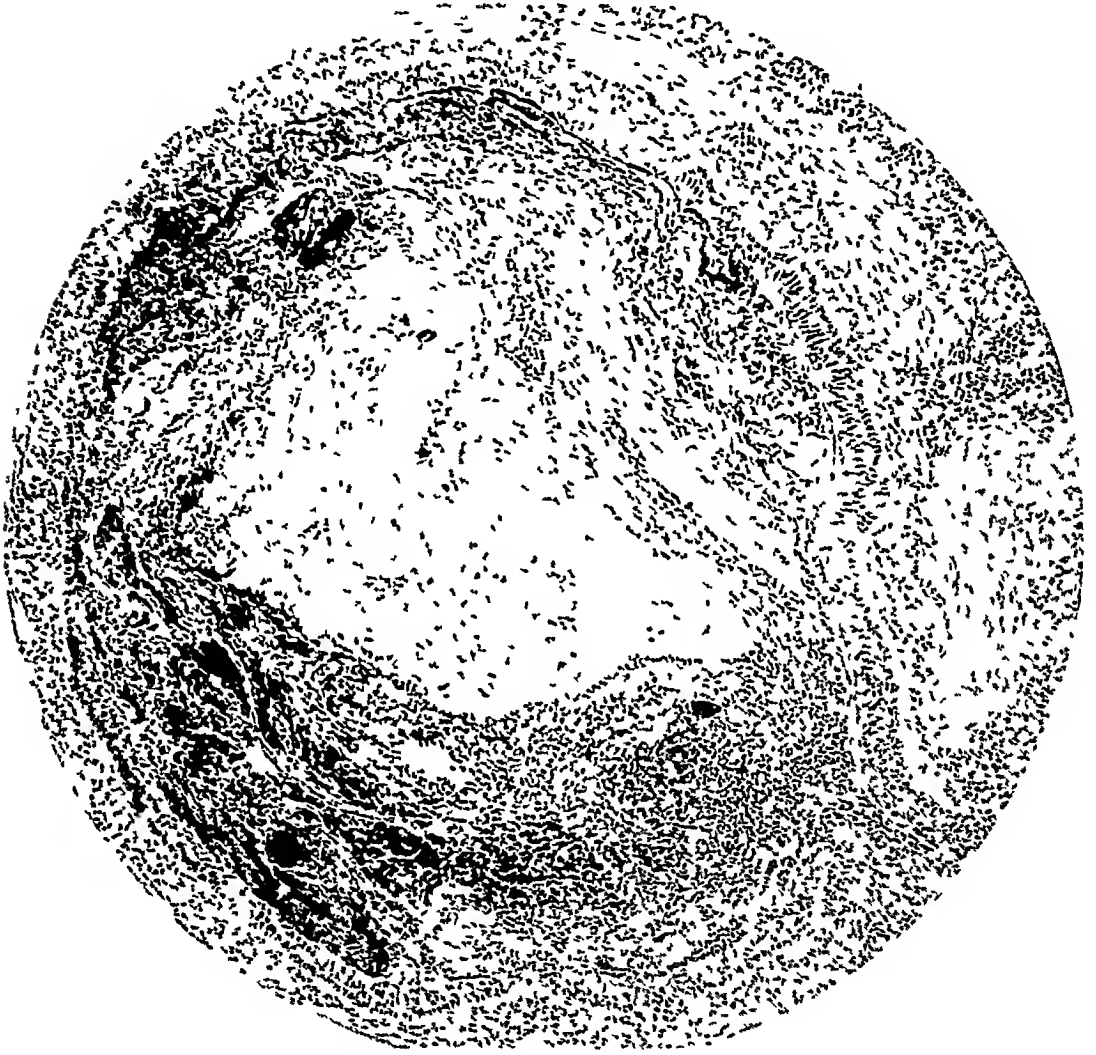


FIG. 4 Bronchiole containing mucopurulent plug in which are found numerous eosinophilic polymorphonuclear leukocytes

of the terminal bronchioles were more prominent than usual and from their lumina mucinous plugs were expressed. Local areas of pneumonic consolidation were scattered throughout both organs. Mucinous material was found in the larger bronchi but did not occlude the lumina. Histologically, the alveolar spaces in some areas were few in number and of great size. Many of the intervening septa had broken. The walls were thin and their capillaries were collapsed (figure 5). Scattered throughout were patchy areas in which the alveoli were filled with inflammatory exudate consisting of neutrophilic leukocytes, many eosinophilic leukocytes, and fibrin. Adjacent to these areas were often seen strands of fibrin into which fibroblasts were

infiltrating in places completely replacing the exudate in the alveoli (figure 6). Lymph vessels were frequently plugged with a cellular exudate consisting almost entirely of eosinophilic leukocytes. Branches of the pulmonary artery had a thickened intima owing primarily to a proliferation of the fixed intimal cells together with a moderate infiltration of the interspaces by eosinophilic leukocytes. Occasionally thrombi were found in the smaller branches of the pulmonary arteries. The bronchial

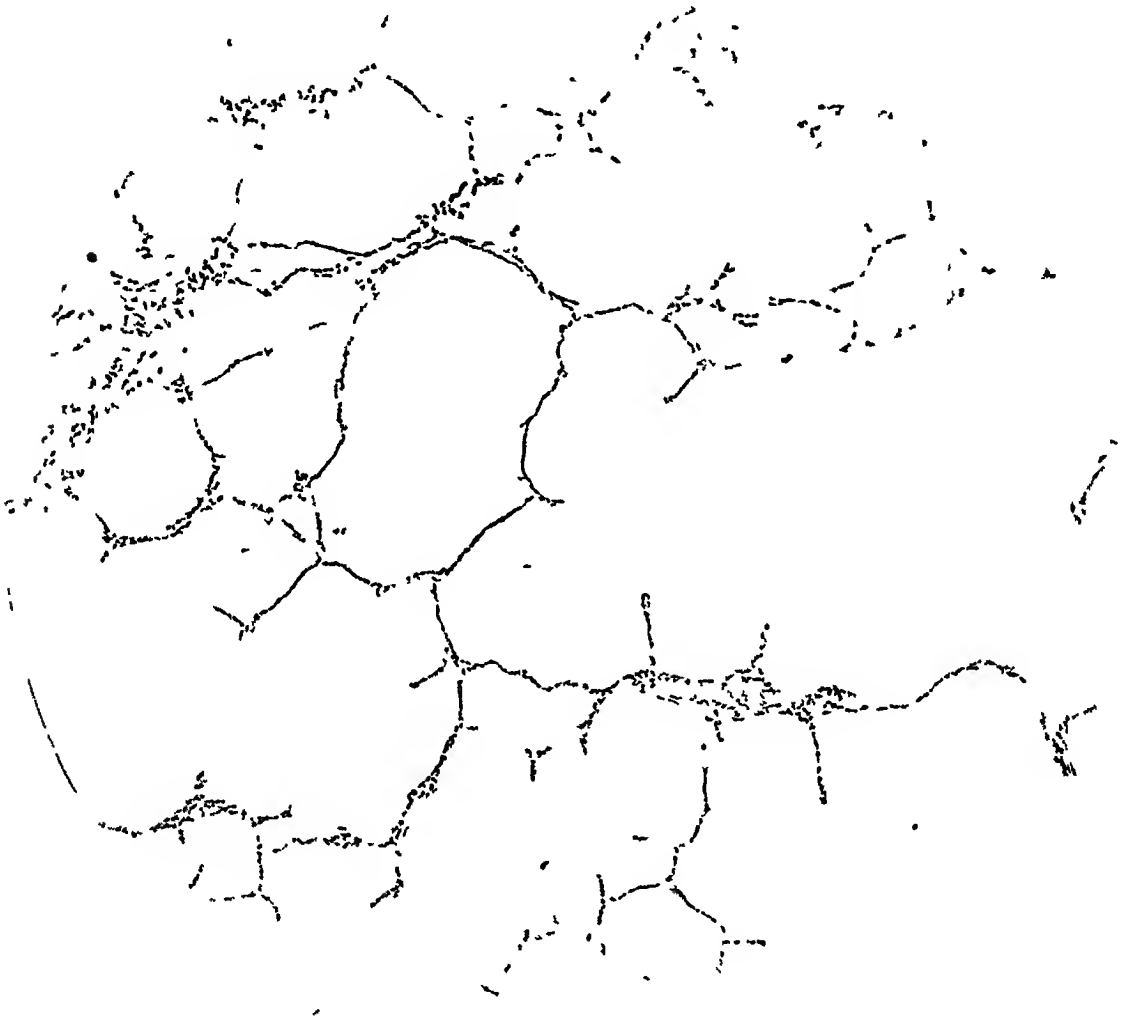


FIG 5 Pulmonary emphysema

mucosa was thrown into many folds, and the lumina were often filled with mucus with and without a cellular exudate (figure 4). The mucosal epithelium in many areas had undergone squamous metaplasia or was desquamated or consisted of low cuboidal epithelium. The basement membrane was well defined, in places hyalinized, and measured up to 32 micra in thickness. The bronchial glands were distended with abundant deep staining basophilic mucus resulting in obliteration of the cell outline and of the lumina of the glands. The smooth muscle of the bronchial tree was not appreciably thicker than that of controls (figure 3).

The marrow from the lumbar vertebra was red and granular, whereas that taken from the upper third of the humerus was red and soft in consistency. Microscopically, the quantitative relationship between hemopoietic and fatty tissue was within the average range. A differential count revealed that the eosinophilic myelocytes, metamyelocytes, and leukocytes were 22 per cent of the total nucleated cells in the bone marrow (figure 1).



FIG 6 Organizing pneumonia. Fibrous tissue may be seen growing into some of the alveolar spaces.

Pathological Diagnosis Bronchial asthma (clinical), pulmonary emphysema, chronic bronchitis, bronchopneumonia, acute diffuse myocarditis with marked infiltration by eosinophilic leukocytes, eosinophilia of the bone marrow, cardiac hypertrophy and dilatation of right ventricle, and obesity.

Case 2 W. K., white male, aged 38, was admitted March 3, 1934.

History The patient first noted frequent nasal and sinus inflammation about 10 years before death. These gradually took the form of asthmatic attacks with fre-

quent exacerbations of symptoms which gradually became worse and refractory to treatment. Frequent trips into warm dry climates were without benefit. There were three of four siblings with hay fever or asthma.

Physical Examination. On the day of admission the temperature was 98 to 99° F., pulse 110 to 130, respirations 20 to 35, and the blood pressure 120 mm Hg systolic and 80 mm diastolic. The patient was a poorly developed, greatly emaciated male in severe asthma. All teeth had been removed. The heart sounds were not remarkable. The chest findings were typical of asthma.

Laboratory Findings. The white blood count was 12,500. The differential count showed neutrophilic leukocytes 76 per cent, lymphocytes 24 per cent, eosinophilic leukocytes 0 per cent.

Course. The patient was given adrenalin, oxygen and morphine with little effect upon his asthma. Sudden death occurred on the fourth hospital day.

Postmortem Examination. The heart weighed 330 gm., and the myocardium was red and coarsely striated. The right ventricle was 3 to 4 mm. in thickness, and the left 11 mm. There was moderate atherosclerosis of the coronary arteries. There was some fibrosis of the myocardium in the region of the papillary muscles. Microscopically, infiltration by inflammatory cells was observed. The coronary arteries showed slight intimal thickening.

The right lung weighed 660 gm., and the left 350 gm. The organs were voluminous, pale gray in color, crepitation was marked, and there were some bullous-like sacculations scattered over the surface. The bronchi were dilated but not sacculated, and contained a semi-thick yellowish-gray mucoid material. Several sections microscopically showed dilated bronchi partially filled with mucopurulent debris containing a few eosinophilic leukocytes. There was slight thickening of the basement membrane, with peribronchial fibrosis and moderate lymphocytic and plasma cell infiltration, but no apparent variation in the size of the bronchial musculature. The openings of the mucous glands were fairly prominent, but the glands themselves contained only a slight amount of mucus. The pulmonary arterial branches were unusual in that the intima was thickened and showed a tendency toward rarefaction. The alveolar spaces in many areas were partially filled with neutrophilic leukocytes and large mononuclear cells. In other places the walls had been ruptured and the spaces were large and empty.

No bone marrow was available for study.

Pathological Diagnosis. Bronchial asthma (clinical), pulmonary emphysema, chronic bronchitis, sclerosis of the pulmonary arteries, bronchopneumonia, arteriosclerosis, and fibrous pleurisy.

Case 3. J. P., white male, aged 41, was admitted May 8, 1938.

History. The first admission was in June 1935 following an upper respiratory infection which had brought on an asthmatic attack. The first attack of asthma followed pneumonia in 1926. The second attack occurred in 1930 after a cold. There were 10 admissions to the hospital for relief of asthma in the intervening years. Bronchoscopic lavages gave temporary relief. Lipiodol studies revealed considerable bronchiectasis. The final admission was after five days of status asthmaticus.

Physical Examination. The temperature was 98 to 104.5° F., pulse 70 to 170, respirations 45 to 60, blood pressure 138 mm Hg systolic and 80 mm diastolic. The patient was typical of one seen in status asthmaticus, many rhonchi and coarse râles being audible over both lung fields.

Laboratory Findings. The white blood count was 20,500. The differential count showed neutrophilic leukocytes 86 per cent, lymphocytes 14 per cent, and eosinophilic leukocytes 0 per cent.

Course. Adrenalin, asthimolysin, and morphine were given without relief. Nasal oxygen was administered. The patient died on the second hospital day, having had no relief from his asthma.

Postmortem Examination The heart weighed 270 gm. The right ventricular wall averaged 7 mm in thickness, and the left 14 mm. The right ventricle was dilated. Grossly the organ was otherwise normal. Microscopically, there were no significant changes. There was no inflammatory reaction, and the vessel walls were thin.

Lungs The right lung weighed 630 gm and the left 660 gm. The pleura was covered by dense fibrous adhesions. Numerous emphysematous blebs were present in the apex and anterior margins of the right lung. The lung was abnormally firm and darkly pigmented. The left lower lobe was markedly hyperemic and edematous. The bronchi passing to the posterior portions of the lower lobes measured 2 to 2.5 cm in diameter and those passing to the anterior portions measured up to 1 cm. The cut surface of the lower lobes revealed bronchopneumonia. The upper lobes showed areas of emphysema. The bronchi were filled with a tenacious mucopurulent material. The intima of the pulmonary arteries revealed numerous atheromatous plaques ranging from 2 to 5 mm across. Many sections microscopically showed bronchopneumonia. One of the larger bronchioles showed a hyalinized thickening of the basement membrane which measured up to 30 micra in places. The epithelium was partially desquamated. The smooth muscle was somewhat hypertrophied in comparison with the control specimens. The mucous glands were numerous, and their lumina were distended with a mucopurulent exudate. There was massive infiltration of the tissues of the bronchi and interstitial tissue of the lung by lymphocytes, plasma cells, and moderate numbers of eosinophilic leukocytes. There was some peribronchial increase in fibrous tissue. The lumina of the bronchi contained varying quantities of mucopurulent material. The medium and large sized arteries showed marked intimal thickening and atheromatous rarefactions, and their walls were infiltrated by a few lymphocytes and plasma cells.

The bone marrow from the lumbar vertebra and sternal body was red and hyperplastic. Marrow from the upper third of the humerus was red at the periphery and fatty centrally. Bone marrow differential count revealed 17 per cent eosinophilic myelocytes, metamyelocytes, and leukocytes. The other constituents of the marrow fell within the normal range.

Pathological Diagnosis Bronchial asthma (clinical), chronic bronchitis, pulmonary emphysema, bronchiectasis, chronic pneumonitis, bronchopneumonia, hypertrophy and dilatation of the right ventricle, arteriosclerosis of the pulmonary arteries.

Case 4 J. G., white male, aged 70, was admitted March 5, 1934.

History Three years after an attack of pneumonia at the age of 15 the patient had his first asthmatic attack. Since then, with the exception of a 10 year period, he had had perennial asthma occurring in unseasonable weather and as often as once a week. For two or three years preceding death he suffered from "smothering attacks," not accompanied by pain, which were so severe as to cause him to jump out of bed. Increasing edema of the extremities was described.

Physical Examination The temperature was 98 to 101° F, pulse 100, respirations 20 to 50. The patient was markedly cyanotic, dyspneic, and emaciated. The chest was barrel-shaped, with poor expansion. The heart sounds were normal. There was dullness at the right base, with wheezing respirations. Marked pitting edema of the lower extremities and the back was found.

Laboratory Findings White blood count was 13,000. No differential count was recorded.

Course Venesection on two occasions and nasal oxygen did not stop an unfavorable course with death on the third hospital day.

Postmortem Examination The heart weighed 400 gm. The left ventricle measured 18 mm in thickness and the right 16 mm. The right auricle and ventricle appeared dilated. There was some thickening along the line of contact of the leaflets of

the mitral and tricuspid valves and of the cusps of the aortic valve. There were some atherosclerotic plaques of the intima and narrowing of the lumen of the coronary arteries. Histologically, there was intimal thickening of the coronary arteries, but there was no inflammatory change in the myocardium.

The right lung weighed 720 gm, the left 800 gm. The visceral pleura was 2 to 3 mm thick. There was hypostatic congestion. The bronchi appeared dilated and there was an increase in parenchymatous fibrous tissue. Microscopically, some bronchioles contained cellular and basophilic debris and an occasional neutrophilic leukocyte. There was metaplasia of the lining epithelium of the bronchioles in places. Some of the alveoli contained red blood cells, large mononuclear cells, and occasional neutrophilic leukocytes. Numerous emphysematous areas were found. The mucous glands were distended with mucus, but the basement membrane was not thickened. The smooth muscle was apparently not hypertrophied. Numerous lymphocytes, plasma cells, and occasional neutrophilic leukocytes were infiltrated in the surrounding fibrous tissue. No eosinophilic leukocytes were seen. One or two arterioles showed hyalinization of their walls with atheromatous spaces in the intima.

No bone marrow study was made.

Pathological Diagnosis Bronchial asthma (clinical) emphysema, cardiac hypertrophy (right ventricle), anasarca, fibrous pleurisy, fibrosis of the lung apices, chronic passive hyperemia of internal organs.

Case 5 C. C., white male, aged 34, was admitted August 31, 1938.

History There was a history of asthma since childhood. One week before admission he complained of malaise. There was no definite chill, but progressively severe cough producing rusty sputum was noted.

Physical Examination The temperature was 100 to 104.5° F, pulse 120 to 160, respirations 40 to 55, and blood pressure 118 mm Hg systolic and 70 mm diastolic. There was dyspnea and cyanosis. The entire chest was filled with coarse râles, and a friction rub at both bases was heard. Heart sounds were indiscernible.

Laboratory Findings The white blood count was 18,500. The differential count showed neutrophilic leukocytes 95 per cent, lymphocytes 5 per cent, and eosinophilic leukocytes 0 per cent.

Course In spite of oxygen and other supportive measures the patient grew steadily worse and died on the third hospital day.

Postmortem Examination The chest was barrel-shaped, the anterior-posterior diameter being greater than the transverse diameter.

The heart weighed 400 gm. The left ventricle averaged 20 mm in thickness, the right 7 mm. The trabeculae carneae and papillary muscles were definitely thickened on the right. The intima of the coronary arteries was thin and smooth except for an occasional yellow plaque. Histologically, near the endocardial surface there was mild myocardial fibrosis. There were collections of lymphocytes, plasma cells, and a few neutrophilic leukocytes in some of the intermuscular spaces. No eosinophilic leukocytes were seen. The fibers seemed increased in size, with evidence of degeneration in places.

The right lung weighed 1130 gm, and the left 1120 gm. The anterior two-thirds of the right and left lower lobes and the entire right and left upper lobes were large, firm, and non-crepitant. The cut surface was red, gray, and moist, and the bronchi were filled with reddish pink frothy material. Histologically, the vessels were congested, and the alveolar spaces were partially obliterated by neutrophilic leukocytes and large mononuclear cells. There was no significant increase in fibrous tissue, but one small bronchiole was seen and its mucosa was considerably desquamated. The walls were not noticeably thickened and the basement membrane could not be delineated. No bronchial glands were included in the one section available for study.

Bone marrow from the lumbar vertebra and the upper third of the humerus was red. The differential count revealed the eosinophilic myelocytes, metamyelocytes, and

leukocytes to be 22 per cent of all nucleated marrow cells. The remainder of the elements were within the average range.

Pathological Diagnosis Bronchial asthma (clinical), bronchopneumonia, serofibrinous pleurisy, acute non-suppurative myocarditis, and hypertrophy of the right ventricle.

Case 6 F M, white male, aged 60, was admitted June 15, 1939.

History The first admission was in 1933 with a history of asthma for the preceding 10 to 15 years. Frequent attacks had occurred but were without serious effect until four days prior to his final admission when he noted pain in the left chest which remained throughout most of the night. This was accompanied by wheezing and fever. He had had a sinusitis in the past. Dependent edema had been present for the preceding four years.

Physical Examination On admission the temperature was 103° F, pulse 120, respirations 24, and blood pressure 140 mm Hg systolic and 84 mm diastolic. There was a paroxysmal cough occurring about every 15 minutes during the examination. There was moderate dyspnea, and the expiratory phase of respiration was emphasized. There were many moist râles and rhonchi over the lungs. Heart sounds were not remarkable. Varicosities and pitting edema were observed in both legs.

Laboratory Findings The white blood count was 21,000. Differential count showed the neutrophilic leukocytes to be 80 per cent. No eosinophilic leukocytes were recorded.

Course Three days after admission the patient developed a sudden rise in temperature to 105° F, pulse to 145, and respirations to 40. Bronchoscopy and aspiration of heavy mucopurulent secretion from the trachea and right bronchus resulted in dramatic relief of symptoms. Two days later he became irrational, developed signs of pneumonia over the right base, and died on the eighth hospital day with a temperature of 106° F.

Postmortem Examination The heart weighed 410 gm. The left ventricle averaged 16 mm in thickness and the right 5 mm. There was moderate arteriosclerosis of the coronary arteries. The papillary muscles were hypertrophied. There was fusion at the commissure of the left and right coronary cusps of the aortic valve and associated with this there was calcification at the bases of these cusps. Histologically, the myocardial fibers were uniform in size and were not enlarged. No inflammatory reaction was seen.

The right lung weighed 1200 gm, and the left 700 gm. They were airless and of rubbery consistency. The bronchi showed areas of dilatation. Histologically, many sections showed hemorrhage into the alveoli and many patches of bronchopneumonia. There were areas of emphysema. Several of the larger bronchioles showed nearly complete mucosal desquamation with thickening and hyalinization of the basement membrane but no mucous plugs. There were numerous lymphocytes, plasma cells, and some eosinophilic leukocytes in the mucosa. The smooth muscle, although fairly prominent, showed no apparent variation from the controls. The bronchial glands showed moderate distention with basophilic staining material which partially obliterated the cellular outline. There was interstitial fibrosis of the lung with lymphocytic and plasma cell infiltration.

The marrow from the lumbar vertebra and the upper third of the humerus was red. Histologically, the cell constituents fell within the normal range, since the differential count of the nucleated cells revealed the eosinophilic myelocytes, metamyelocytes, and leukocytes to be 14 per cent of the total.

Pathological Diagnosis Bronchial asthma (clinical), pulmonary emphysema, chronic interstitial pneumonitis, bronchopneumonia, chronic bronchitis, and generalized arteriosclerosis.

TABLE I

	I	II	III	IV	V	VI
HISTOLOGICAL FINDINGS	Moderate	Marked	Marked	Present, moderate	Slight (1 section) Insufficient data (1 section)	Present
Pulmonary emphysema	Extensive organized pneumonitis	None	Interstitial pneumonitis Organizing pneumonia	None	Insufficient data	Interstitial pneumonitis Organizing pneumonia—early
Chronic pneumonitis	Extensive Slight	Present Moderate	Present Marked	Present Slight	Insufficient data	Present None
Chronic bronchitis	Extensive Present	Present None	Present None	Present None	Present Insufficient data	Present None
Pulmonary arteriosclerosis	Thickened	Slight	Thickened	None	Insufficient data	Thickened
Acute bronchopneumonia	?	None	?	None	Insufficient data	Normal
Pulmonary endarteritis (active)	Present	Moderate number of bronchi filled with mucus	Present	None	Insufficient data	None
Thickening of basement membrane	Marked	None	Slight	None	None	Moderate
Hypertrophy of bronchial musculature	Dilated only	Dilated only	Dilated only	Slight	—	Marked
Mucinous plugs in small bronchi	Bronchial glands distended with mucus	Essentially normal	Bronchial glands distended with mucus	No bronchial glands in sections	Insufficient data	None
Eosinophilic infiltration of peribronchial tissues	Acute diffuse myocarditis with infiltration by large numbers of eosinophiles	None	None	None	Non-suppurative myocarditis	None
Sacculation of bronchi	22%	—	17%	—	22%	14%
Distention of bronchial glands and ducts with mucus	14%	0	0	Not done	0	0
Myocarditis						
Eosinophilic, myelocytes, metamyelocytes and leukocytes in bone marrow						
Eosinophilia in blood						

DISCUSSION

The essential findings in each case are tabulated in table 1. The last two cases are included as asthmatics who died from pneumonia, the fourth died in cardiac failure. As already noted, the material for study in Case 5 is limited, but it was included because of the cardiac findings. Excluding that case for a moment, we note that pulmonary emphysema, chronic bronchitis, and bronchopneumonia were present in each case, and pulmonary arteriosclerosis in all but the last. Cor pulmonale was present in two. In one (Case 1) the well developed right ventricular hypertrophy was secondary to the chronic pneumonitis, and in the other (Case 4) a longstanding emphysema accounted for the enlargement. Thickening of the basement membrane was present in all but the fourth case. Mucous plugs in the small bronchi were present in two instances, distention of the glands with mucus in three, eosinophilic leukocytic infiltration of the peribronchial tissues in four, and dilatation of the bronchioles in four. Pulmonary endarteritis was noted in but one case. Hypertrophy of the bronchial musculature has often been cited as one of the necessary criteria in making the pathological diagnosis of asthma^{2, 3, 4, 5}. We compared our microscopic sections with those obtained from patients who had died from other than pulmonary diseases. It was our impression that, in our series, there was no appreciable variation in the size of the smooth muscle bundles. At the same time we measured the thickness of the basement membrane in the controls and found it nowhere to be more than 16 micra, a figure which was exceeded in our series as noted above.

For the past three years the Pathology Service has been doing routine bone marrow studies on all cases. In order to obtain an accurate evaluation on the four cases in our series, one of us (J. R. R.) counted not less than 1000 nucleated cells in each instance. Two counts of 500 cells each that checked were accepted. For controls similar counts were made from 10 normal cases. These slides were obtained from patients who had died a traumatic death and who exhibited no pathologic change other than that incurred by the accident. The counts of eosinophilic cells obtained from this normal group were found to range between a maximum of 3.96 per cent and a minimum of 0.6 per cent with a mean value of 2.26 per cent. Comparing these figures with those noted in the series it is interesting to find that three of the four cases studied have values that fall well within the normal range. It is regretted that only two of these four cases died a truly asthmatic death, but the findings in these two cases in the light of the control group are significant. In one instance (Case 3) a count of 1.7 per cent was obtained, and in the other (Case 1) the count was 2.2 per cent (figure 1). This patient was the only one in which an eosinophilia (14 per cent) was recorded in the peripheral blood stream. Nothing was found in the literature to explain the amazingly high eosinophilia found in the marrow. It certainly is not a consistent finding in asthmatic fatalities, as we have shown. On the other

hand, it may be present in cases in which there is a peripheral eosinophilia from any cause. One must withhold any conclusions until further bone marrow studies have been performed and merely state that this finding of an eosinophilia in the bone marrow of asthmatic patients is unusual.

In Case 1, along with an eosinophilia in the bone marrow, there was noted an infiltration of numerous eosinophilic leukocytes into the myocardium and lungs as part of the inflammatory reaction in these organs. The pathological picture could not be duplicated in asthmatic cases in the literature. Karsner, in his textbook,⁶ discusses a type of myocarditis following pneumonia and other infectious diseases. The description does not correspond with the findings in our case. Boyd⁷ describes an acute parenchymatous myocarditis following such toxic conditions as diphtheria. Although he notes that if death occurs early in the disease there is no inflammatory change, he does not detail the findings seen by us. In one report⁸ two cases of syphilis were described in which there was an eosinophilic leukocytic infiltration of the myocardium following treatment with salvarsan and bismuth. Although the author found areas of necrosis in the muscle somewhat similar to our findings, yet the lesions themselves contained giant cells, and were described as being tuberculoid in appearance. He favored the view that this eosinophilic myocarditis was allergic in origin. One case in our series, in which there was found a non-suppurative myocarditis, had a long asthmatic history and hence is of value for comparative purposes. In this case (Case 5) the cellular response of lymphocytes, plasma cells, and large mononuclear cells, although typical of that described by the textbooks, is entirely different from that seen in our first case (figure 2) in which the eosinophilic leukocytes are not only the predominating cell in the necrotic areas, but also are found in large numbers elsewhere in the myocardium.

It is possible again to conjecture that this reaction is concomitant with a general peripheral eosinophilia. It also may be present during an attack of asthma in which the blood eosinophilic count is elevated, only to disappear along with some of the other pathologic findings as was suggested by Thieme and Sheldon.⁴ Further study will have to be done to clarify this issue. Certainly at the present time it appears to be a very rare condition.

SUMMARY

Six cases of bronchial asthma with autopsy findings are presented. Three of these died in status asthmaticus. The majority of the anatomical lesions described in asthma were present. Bone marrow studies are described in four cases. In one case which had a large preponderance of eosinophilic myelocytes, metamyelocytes, and leukocytes in the bone marrow, there was also found an acute diffuse myocarditis with tremendous infiltration of eosinophilic leukocytes. A review of the literature has not revealed any report of similar bone marrow or myocardial findings in fatal asthma.

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FAT EXCRETION IN THE BOWEL OF MAN^{*}

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IN general it has been thought that the fat and fatty acids found in feces represent unabsorbed fat of food. In recent years, some changes in this point of view have occurred. Hill and Bloor,¹ in 1922, found that certain portions of the fat in the feces of dogs were of the type excreted by the intestinal tract. In 1924, Sperry and Bloor² demonstrated that fat appeared in the feces of cats and dogs on a fat-free diet. This was confirmed by Holmes and Kerr,³ in 1923. Sperry⁴ and Sperry and Angevine⁵ concluded that desquamation of intestinal epithelium was not an important source of these lipids and that when dogs received a lipid-free diet the amount of lipids excreted from ileac fistulas was much greater than the amount excreted in the feces. Previously, Beumer and Hepner⁶ and Burger and Oeter⁷ found that the amount of cholesterol in the intestinal contents was greater in the colon than it was in the ileum of dogs and cadavers. In 1934, Kiakower,⁸ who studied 20 normal persons, assumed that when fat was given in moderate amounts the fecal lipids did not represent a residue of unabsorbed fat but probably represented an excretion of the lipids of the blood into the intestinal tract. Finally, as a result of study of a patient who had a fistula of the ileum, Doubilet and Reiner⁹ concluded that the ileum secreted a fluid which contained about 2 per cent of lipids.

METHOD AND RESULTS OF OBSERVATION

In order to obtain more information about the excretion of fat by the intestine of man, observations were made on 14 human beings. Subject 1 had undergone an ileocolostomy and resection of the right portion of the colon and subject 2 had undergone an ileocolostomy. The observations on subjects 1 and 2 were made about 20 days after the respective operations had been performed. Subject 3 had undergone an ileostomy and subsequent resection of the right half of the colon and approximately four inches of the terminal portion of the ileum. Subjects 4, 5, 6, 7 and 8 had thrombo-ulcerative colitis which involved the entire colon. Subjects 9 and 10 were normal persons who received a fat-free diet. Subjects 11, 12, 13 and 14 had thrombo-ulcerative colitis.

Subject 1 received a fat-free diet for 10 hours, all food was withheld for 14 hours before the diet was given and for 14 hours after the diet was discontinued. Subjects 2 and 3 received a fat-free diet for 36 hours, but all

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Work done on Intestinal Service, St Mary's Hospital

† From University of Cordoba, Argentina

food was withheld for 12 hours before the diet was administered. In the observations made on subjects 4, 5, 6, 7 and 8 the dietary regimen was the same as that used for subject 1. Subjects 9 and 10 received a fat-free diet for 84 hours. Subjects 11, 12, 13 and 14 received a high-fat diet. Previous analyses had disclosed that the intestinal excretion of fat by these four subjects was within normal limits when a regular diet was administered. The observations on subjects 11, 12, 13 and 14 were made to determine the effect of a high-fat diet on the intestinal excretion of fat by patients who have thrombo-ulcerative colitis. This was done for the purpose of determining the excretion of fat in cases in which a high-fat diet was received.

The fat-free diet was made up of vegetables and fruits, sugar, jelly and candy. It furnished approximately 2000 calories in 24 hours (table 1) and contained approximately 1.65 gm. of fat.

Carmine was administered one hour before the first meal and immediately after the last meal of the fat-free diet. Charcoal was given with the first meal after the fat-free diet had been discontinued. After the administration of the first dose of carmine, each stool that contained the dye was collected in a special box marked with the date and time of passage. Some of these were examined separately, some were collected, mixed and analyzed as one specimen, as the data obtained from single stools and mixtures of the stools of any given subject were entirely comparable. Care was taken to avoid contamination with urine. Gauze was used to receive the excreta of subject 3, from the ileac stoma. In all observations the collection of feces and ileac discharges was continued until the appearance of the charcoal, and each stool passed was inspected for carmine and charcoal. The specimens were preserved in the refrigerator when they could not be examined immediately.

The amount of total fat in the feces was determined by the Fowweather⁸ modification of Saxon's method. All results were calculated in terms of percentage of the dry feces.

The observations on subjects 11, 12, 13 and 14 were made while the subjects were receiving a high-fat diet. Two observations were made on subject 11, the first, while the patient had generalized edema. During each observation the patient received 120 gm. of fat daily. The stools that were passed during each observation were mixed and were examined as a single specimen. The value for the total fat in the mixed specimen of the stools that were passed during the first observation was 29.7 per cent of the dry matter. The second observation on subject 11 was made after the edema had decreased and disclosed 21 per cent of dry matter, 13.8 per cent of which consisted of fat.

Subject 12 received approximately 185 gm. of fat daily, 9.5 per cent of the dry matter in the mixed specimen of stools consisted of fat.

Subject 13 received 200 gm. of fat daily. A mixed specimen of the stools contained 12 per cent of dry matter, 10.2 per cent of which consisted of fat.

TABLE I
Intestinal Excretion of Fat (14 Cases)

Subject		Conditions of Experiment	Dry Matter, Per cent of Stools Examined	Total fat,* Per cent	Fat, Gm	Neutral fat,* %	Fatty Acids,* %	Soap*
No	Condition							
1	Ileocolostomy and resection of right half of colon	Fasted 11 hours, fat-free diet 10 hours and then fasted 14 hours	18.6	1.21	2.76	0.101	1.136	
2	Ileocolostomy	Fasted 12 hours, fat-free diet 36 hours	Second stool, 7.2 Third stool, 6.8 Fourth stool, 6.4 Fifth stool, 20.8	Second stool 0.72 Third stool 0.4 Fourth stool, 0.41 Fifth stool 1.48	3.76	0.12	1.1	
3	Ileostomy and resection of right half of colon and terminal portion of ileum	Fasted 12 hours, fat-free diet 36 hours	First spec 6.3 Second spec 6.3	First spec 0.4 Second spec 0.36	5.75	0.25	0.11	
4	Thrombo-ulcerative colitis	Fasted 12 hours, fat-free diet 36 hours	Second, third, fourth and fifth stools 6.0	1.0	4.8			
5	Thrombo-ulcerative colitis	Fasted 12 hours, fat-free diet 36 hours	Second, third, fourth stools, 7.6 Fifth and sixth stools, 8.0	0.40 0.6	4.6	0.133 0.177	0.227 0.223	0.04 0.20
6	Thrombo-ulcerative colitis	Fasted 12 hours, fat-free diet 36 hours	Four stools, 5.0	0.96	3.84	0.354	0.223	0.38
7	Thrombo-ulcerative colitis	Fasted 12 hours, fat-free diet 36 hours	All stools mixed	1.08	4.0	0.398	0.272	0.41
8	Thrombo-ulcerative colitis	Fasted 12 hours, fat-free diet 36 hours	Second, third, fourth stools, 9.18 Fifth, sixth and seventh stools, 9.0	0.6 0.4	4.5	0.34	0.26	
9	Normal person	Fasted 12 hours, fat-free diet 36 hours	First stool, 21.24 Second stool, 29.24	1.4 1.34	14.0	0.31 0.66	1.43 0.62	0.66 0.06
10	Normal person	Fasted 12 hours, fat-free diet 36 hours	First stool, 18.4 Second stool, 32.0	1.20 0.94	10.7	0.45 0.14	0.51 0.66	0.24 0.14
11	Thrombo-ulcerative colitis	Fasted 12 hours, 120 gm fat given daily Patient had edema, 3+	Stools mixed during edema After edema decreased, 21.0	29.7 13.8	70.5			
12	Thrombo-ulcerative colitis	Fasted 12 hours, 185 gm fat given daily	Stools mixed	9.5	38			
13	Thrombo-ulcerative colitis	Fasted 12 hours, 200 gm fat given daily	Stools, 12	10.2	24.4			
14	Thrombo-ulcerative colitis	Fasted 12 hours, 120 gm fat given daily	Stools mixed	3.24	12.7			

* Expressed in percentage of dry matter

In observing subject 14, who received a high-fat diet, the stools were mixed and were examined as a single specimen, 3.24 per cent of the dry matter in this specimen consisted of fat.

COMMENT

The number of observations reported is small, but we believe that the results are of value in confirming those obtained on animals and that they indicate a significant variation in the excretion of fat under different circumstances. Excretion of fat by normal persons was greater than excretion of fat by patients who had been subjected to resection of the right portion of the colon. Furthermore, excretion of fat by patients who had thrombo-ulcerative colitis was less than excretion of fat by normal persons, but was greater than excretion of fat by the patients who had been subjected to resection of the right half of the colon.

It is true that the amount of fat in the feces of the subjects who received a fat-free diet varied, but an average of 0.79 per cent of total fat was excreted by persons who had been subjected to an ileostomy or an ileocolostomy, an average of 0.81 per cent was excreted by persons who had thrombo-ulcerative colitis, and an average of 1.23 per cent was excreted by normal persons, however, the deviation from the averages is considerable. These facts would suggest that the large intestine itself plays a part in the excretion of fat and that the greatest excretion occurs in the proximal segments of the large intestine. The entire intestinal wall is injured in cases of thrombo-ulcerative colitis. It has been pointed out previously by Curry and Bergen⁹ and by Whittaker and Bergen¹⁰ that the colon serves both as a secretory and excretory organ.

Verzár and McDougall¹¹ expressed the opinion that absorption of fat does not take place in the cecum. They said that "practically all the fat ingested is absorbed by the time chyme enters the large intestine, and no fat whatever seems to be absorbed there." Welch, Adams, and Wakefield¹² did not find any change in the absorption of fat in cases of thrombo-ulcerative colitis and they suggested that fat is not absorbed in the colon. Satisfactory proof that absorption of fat occurs in the cecum does not exist. However, the suggestion that excretion of fat occurs in the cecum and ascending colon seems clear.

It is noteworthy that in cases in which the amounts of neutral fat, fatty acids and soap were determined, the excretion of fatty acids was greater than that of neutral fat. This may be the result of normal digestive processes or the result of an unexplained activity of the mucosa. In this connection it may be well to remember that Brown, Hansen, McQuarrie and Burr¹³ pointed out that in one case the concentration of fatty acids in the serum was lower when the intake of fat was 2 gm per day for a period of more than six months than it was when the patient received a normal diet.

CONCLUSION

Excretion of fat by the intestine occurs when human beings receive a fat-free diet. This is suggestive of the possibility that the intestinal wall secretes fat. Our studies suggest that the large intestine excretes more fat than the small intestine. In cases of thrombo-ulcerative colitis the average excretion of fat is lower than the average excretion of fat by normal persons. This may be the result of injury of the intestinal wall.

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SOME NOTES ON CYSTIC DISEASE OF THE LUNGS, WITH A REPORT OF ONE CASE*

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It is our purpose to report a case involving the diagnosis of cystic disease of the lungs. Clinically, this case was diagnosed as congenital cystic disease of the lungs, but even with all the data before us, we wish to emphasize how difficult it is to make a definite differential diagnosis between congenital cystic disease of the lungs, acquired cystic disease of the lungs, and extensive



FIG 1 7-11-32 Reëxamination of the films of the shoulder made in 1932 showed some bullae which were overlooked in the first examination

emphysema with bullous formation. The case is reported with its clinical and pathological findings. Roentgenograms of the lungs and also some actual photographs are shown.

In a case of multiple cyst-formation in the lung, the diagnosis might seem to be of academic interest only, because of the small likelihood that this type

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of case could be benefited by surgery. Since the literature of the subject, however, shows that some types of cystic disease of the lungs are amenable to surgical procedure, it is of definite importance to differentiate these conditions.

CASE REPORT

C. J. I., aged 34, negro male, came in May 14, 1939, complaining of shortness of breath and indigestion. About four years previously he began to notice shortness of breath on exertion. His indigestion began about the same time. In late December



FIG 2 1-21-37 (A-P view) The appearance is that of congenital cystic disease of the lung. The diaphragms are quite low and limited in mobility, and there are questionable small amounts of fluid at both costo-phrenic angles.

of 1937, he had an attack which his doctor diagnosed acute indigestion. He had been constipated for three days when he began to get pain in his abdomen and cardiac palpitation. He then became dizzy, began to perspire, and finally lost consciousness for a short time. He was very weak from this attack for several weeks. He continued to be short of breath and was conscious of palpitations and what he described as "heart flutter." He was sent to the hospital in November of 1938, and it was there found that he was quite anemic. He received two transfusions. About that time he noticed some swelling of the ankles. In February of 1939 he had influenza, and had become gradually more short of breath since that date until he was finally

not able to lie down in bed. He had a very annoying non-productive cough, if this occurred while he was lying down, he almost smothered. This caused him to be afraid to lie down. At times he sat up all night, being most comfortable when he leaned forward. During the preceding two years he had lost 40 pounds, for even small amounts of food caused gas, and this in turn produced dyspnea. He had no hemoptysis. He had some pain in the left chest in February, which the doctor diagnosed as pleurisy.



FIG 3 (A-P view) Reëxamination of the chest shows an increase in the extent of the process. There is only a small amount of lung tissue on the right, but slightly more on the left.

There were no night sweats. He had a slight wheezing at times. The rest of the history was practically negative, except that the patient stated that he had been quite athletic in college, being a long-distance runner and a football player. He further stated that he had had no dyspnea at that time. He drank heavily during 1937 and up until October of 1938. His family history was negative. His wife and three children were living and well.

Physical Examination The patient had marked dyspnea which was increased by talking and also by movement of any kind. The head showed no gross abnormalities. The eyes were slightly prominent, the pupils were small but reacted to

light normally. Ocular movements were normal. The nose was unobstructed. Hearing was intact. Many of the posterior teeth had been removed. The gums showed some gingivitis. The tongue was moderately coated. The tonsils were back of red pillars. The neck showed some posterior cervical adenopathy. Veins of the neck were engorged. There was a three-inch operative scar over the outer end of the right clavicle, extending over the right shoulder. The chest showed expansion to be poor and equal. There was some retraction above and below both clavicles. There was some fullness of veins over the upper arms, more marked on the right. Little

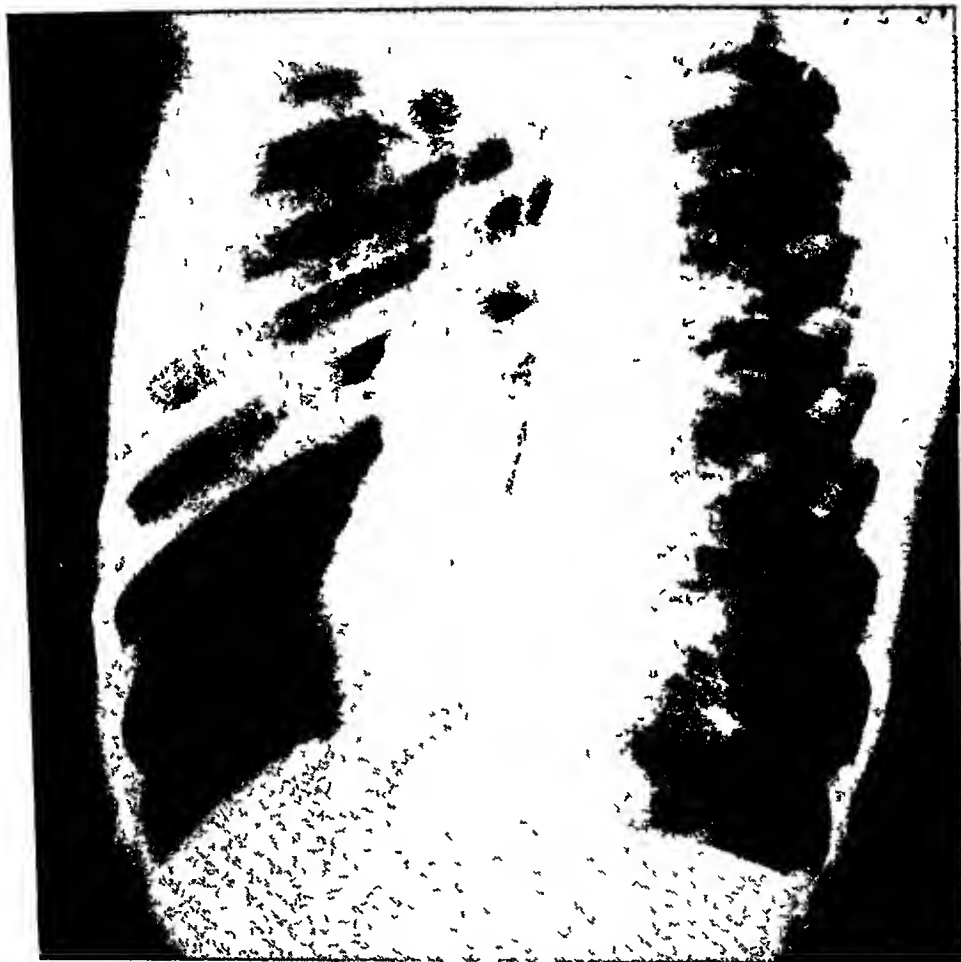


FIG. 4 7-6-39 Oblique view

if any movement of the diaphragm was made out. The percussion note over both upper lungs, front and back, was high pitched. It was more resonant over lower lungs, and seemed to be more resonant during inspiration. Breath sounds were markedly suppressed. Whispered voice was not increased. Tactile fremitus was present. The spoken voice seemed to be increased over both lungs. Examination of the heart showed the left border to be 7 cm. from the midline, and the right border to be 2.5 cm. from the midline. There was a diffuse cardiac impulse in the epigastrium. Blood pressure in the left arm was 114 mm Hg systolic and 75 mm diastolic, and in the right, 110 mm systolic and 80 mm diastolic. The rate was 108, and regular. There were no murmurs, and the sounds were of good quality, being heard best in the epigastrium. The abdomen was not remarkable except for a definite bulging of the upper right rectus muscle. There was marked tenderness in this region. There was a long

scar on the outer side of the left thigh resulting from operation for fascia graft on his right shoulder. The rectum, genitalia, and extremities were essentially negative.

He was admitted to Duke Hospital on July 3, 1939. The following is a report of the laboratory and roentgen-ray work done on admission.

The blood was within normal limits, urine was negative, sputum was negative for tubercle bacilli. The vital capacity of the lungs was 1.16 liters, 30.4 per cent



FIG 5 The left lung

normal. Roentgenogram of the chest showed "extensive areas of fibrosis throughout both lungs and in the left mid lung, there are definite annular areas, some of which are in the mid lung and others are possibly in the posterior pleura. Throughout the right lung, there are numerous fibrotic bands, or possibly small cystic areas, with collapse of small areas of lung. The diaphragms were quite low and limited in mobility and questionable small amounts of fluid in both costophrenic angles. This has the appearance of congenital cystic disease of the lungs, and is most unusual in its distribution." Electrocardiogram revealed right axis deviation and suggested myocardial damage. Wassermann and Kahn tests were negative.

Course in Hospital On July 9, 1939, an attempt was made to do a diagnostic pneumothorax on the right chest. About 150 cc of air were injected. On the following day some lipiodol was injected, but unfortunately a spontaneous pneumothorax



FIG 6 The right lung (cut surface)

developed on the right side, and the patient became much more dyspneic. The dyspnea was so marked that on the next day it was necessary to insert a trocar and apply continuous suction. This gave him some temporary relief, but his dyspnea gradually increased, and he died on July 14, 1939.

Autopsy Findings The examination was limited to an abdominal incision. However, the heart and lungs were removed sub-diaphragmatically.

Gross Examination Dr. Brodie C. Nalle, Jr. The body was that of an emaciated 34-year-old colored male, weighing 124 pounds, and measuring 5 feet and



FIG 7 The right lung

11 inches in length. Ribs and other skeletal parts were quite prominent. There was an old healed scar over the right shoulder (acromio-clavicular approach). Otherwise, the external examination was negative.

There was
Otherwise,

The abdominal cavity was free from fluid and gas. All peritoneal surfaces were smooth and glistening and every organ appeared grossly normal.

The thoracic cage was entered through the peritoneal surface of the diaphragm. Neither pleural nor pericardial cavities contained any excess fluid. The right lower lobe showed a fibrinopurulent exudate over the base, and, in addition, the basal and parietal surfaces of the lobe were attached to the right dome of the diaphragm and to the lateral chest wall, respectively, by thin fibrous adhesions. The left lung was free of exudate and adhesions.

The right lung weighed 500 grams and the left, 450 grams. On the surfaces of both lungs were multiple emphysematous blebs of variable size and shape; the largest measuring 7 cm in diameter, and the smallest, 7 to 8 mm. These cyst-like sacs covered the lung periphery in grape-like clusters and were formed by a thin, translucent, pleura-like membrane which contained dilated blood vessels. A probe introduced through a bronchus into several sacs failed to collapse them even though they appeared to be air-containing cysts.

The main bronchi were patent, and the bronchial nodes were not remarkable. Sectioning revealed many of the blebs to be of peripheral distribution. These cyst-like structures were present both on the periphery of the lung and also in the lung substance proper. Some were very near the hilus of the lung. The small amount of lung tissue remaining appeared to be free from consolidation and congestion.

Other organs were essentially negative.

Microscopic Examination The significant findings in this case were limited entirely to the lungs. Routine sections (stained with hematoxylin and eosin) revealed marked areas of emphysema and atelectasis throughout the lung. Often large cystic areas surrounded by interstitial tissue were seen. Bronchial epithelium could not be demonstrated as a lining for any of these cysts. Much anthracosis was present which was seemingly engulfed by large mononuclears. Iron stain strengthened the opinion that the pigmented areas were anthracotic. It was thought that the emphysematous blebs might have been caused by a lack of elastic tissue. Elastic tissue stains showed an adequate amount of elastic tissue which had been ruptured in the emphysematous areas.

Bacterial stain of the pleural exudate showed clumps of Gram-positive cocci and singular Gram-positive diplococci. The lung tissue itself was free from bacteria.

Interpretation We have no explanation for this condition in the lungs. There was no history of asthma nor was there any demonstrable bronchitis or other cause which might have produced partial obstruction of the bronchi. Whether this condition started as congenital cysts which opened into bronchi, later becoming air-containing, or finally, whether this picture was produced by a deficiency in connective tissue stroma we are unable to say.

Dr Douglas H. Sprunt was kind enough to review all the pathological material and to revise the pathological report. The following is his interpretation of this review.

"Our interpretation of this case, both from the history and morbid anatomical findings, is that this is one of acquired pulmonary emphysema, for there is nothing in the history to indicate that he had any pulmonary malformation before the age of 30. There is nothing in the history or anatomical findings to explain why this began to develop at this time. All we have is a case of pulmonary emphysema of unknown etiology, but I do not believe it should in any way be confused anatomically with congenital cystic disease of the lung, although it seems to us that the most likely interpretation is that the elastic tissue of the lung was of a poor quality, and, around 30 years of age, had deteriorated to such an extent that it led to this extensive pulmonary emphysema."

DISCUSSION

There has been no effort to make an exhaustive review of the literature, but there has been an effort to look into the question of cystic disease of the lungs with special emphasis on its congenital form. Various individuals have been given credit for reporting the first case, namely, Fontanus in 1638, Bartholinus in 1687, and Meyers in 1858. However, the first comprehensive report of this condition was made by A. R. Koontz in 1925. At this time he collected 108 cases from the world's literature, and added one of his own. Schenck¹ in 1937 stated that 381 cases had been reported, including five of his own. Francis A. Ford² reported a case of a gradually expanding pulmonary cyst in a new-born infant diagnosed by roentgen-ray and confirmed by autopsy.

There are various theories concerning the formation of these cysts. King and Harris³ offer a rather unique explanation. They quote S. S. Simpkins as saying that the bronchi develop as small ramifications of ectodermal tissue which become canalized almost immediately. King and Harris think that an unknown process interferes with this canalization at some point proximal to the termination of that particular ramification, and that this interference results in an occlusion at that point. Beyond this point, canalization begins again, and thus an isolated canalized segment is formed. The mucous membrane of this segment in turn assumes a normal secretory function, and a cyst is formed. Probably the rapidity of the prenatal growth and the size of the cyst at birth are dependent on (1) the amount of functioning bronchial mucosa entrapped, and (2) the capsular strength of the cyst.

The morbid anatomy is described very similarly by various writers. According to Wood⁴ all cases fall into two groups: first, those in which there are single or multiple large cysts containing air or fluid, and second, diffuse degeneration resulting in so-called "honeycomb" type of lung. The cysts themselves may be designated as follows: first, fluid cysts, and, second, air cysts. The fluid cyst is one that has not ruptured into a bronchus. There are two types of air cysts—the non-expansile and the expansile. The non-expansile cyst has a small opening into a bronchus, and air is able to get in and out slowly. Harris and King say that according to Jackson, this small opening represents a bypass valve. The expansile, or balloon cyst has an opening into a bronchus through which the air can enter but through which it cannot escape. Jackson calls this mechanism a "check valve." When the opening from the bronchus is large and free, the cyst usually cures itself. Jackson says that all fluid cysts are caused by stop-valve occlusions.

Cole and Nalls⁵ state that the cyst walls have the characteristics of bronchi, bronchioles, atria, infundibula, or alveoli. The cysts are often traversed by strands of fibrous tissue which gives them the appearance of being trabeculated. Fluid cysts contain gelatinous or albuminous fluid.

which in turn contains desquamated epithelial cells or debris. The wall of the cyst may be thick or thin. This depends on the size of the cavity, the pressure in the cyst, and the presence or absence of infection. Koontz⁴ found the small or medium-sized cavities lined with many-layered ciliated columnar epithelium, whereas the larger cavities were lined with flat or cuboidal cells. External to the mucosal membrane are found elastic tissue, concentric fibers of smooth muscle, and pieces of cartilage. The cysts may contain fluid, fluid and air, or only air. An air cyst may involve one whole lobe, or even an entire lung. It may even press over into the mediastinum and embarrass the other lung. This is characteristic of the balloon cyst with its check valve or ball valve mechanism. This type of cyst ruptures easily and may in this way cause a real pneumothorax.

Cystic disease of the lungs may cover the whole span of life, extending from premature stillbirth to very old age. Koontz says that in a patient who has reached maturity, it is hard to tell whether a cyst is congenital or acquired, but he agrees with other authorities that the lack of pigment in the wall of the congenital cyst is the differential diagnostic point. This point alone shows that the pathological condition antedates birth. If the embryological assumption about these cysts is admitted, then all of them begin as fluid cysts. It would seem that the increasing internal pressure and the strength of the cyst wall would be the main factors in determining when the fluid cyst would rupture into a bronchus. W. Anderson⁷ advances the theory that in the presence of pulmonary infection, the fluid cysts enlarge rapidly and occasionally rupture. He thinks that a coughing seizure may be a precipitating cause.

Gordan⁸ says that if no complication arises, these patients may remain symptom-free for years. The symptoms are usually not diagnostic in character. Authorities agree, however, that recurring attacks of cyanosis and dyspnea in infants and children should suggest the possibility of congenital cystic lung disease. Wood⁹ states that progressive dyspnea with or without preceding infection in an older individual should suggest this condition. He further states that the clinical manifestations of this condition vary greatly, and that their severity depends upon two factors: first, the extent of destruction of parenchymal tissue, and second, the change in intrathoracic pressure. A sudden increase in pressure in a balloon cyst will cause a sudden attack of cyanosis and dyspnea. Expectoration may or may not be a symptom. This depends upon a channel being present between the cyst and the bronchus. Fever is present only when there is infection, and it is seldom very high. Anorexia, palpitation, and vomiting may be present. There may or may not be hemoptysis, and if present, it often raises the question of tuberculosis. Epigastric distress may be marked. There may be great loss of weight. Dehydration and lethargy may be present. Cough may be a marked symptom, and wheezing may occur. In fact, the condition may simulate asthma very closely. Our patient, who

showed many of these symptoms, had been diagnosed and treated as an asthmatic by at least one doctor

The clinical diagnosis is almost entirely dependent on roentgenology King and Harris found only one instance in which the clinical diagnosis was made prior to roentgenologic examination The fluid cysts offer much more difficulty from a diagnostic standpoint than do the air cysts These cases often give the history of having spat up milky or albuminous fluid This happens when a fluid cyst ruptures into a bronchus Kirklin¹⁰ quotes E F Pearson as saying that many cases with congenital cystic disease are wrongly diagnosed acquired bronchiectasis, localized emphysema, or pneumothorax

There are several procedures which may be of help in making the diagnosis Lung mapping with lipiodol may be helpful Induced pneumothorax may help This procedure will often push the cyst wall away from the chest wall, and thus differentiate the condition from pneumothorax Fluid-containing cysts must be differentiated in the main from the following conditions: (a) pulmonary abscess, (b) dermoid cyst, (c) thoracic tumor, (d) echinococcus cyst, (e) empyema, (f) teratoma, (g) chondroma, and (h) ganglioneuroma Freedman¹¹ says that the solitary giant-type cyst is more common in children than it is in adults, whereas in adults, the cysts are more often multiple in type A non-expansile air cyst is usually in the intrapulmonary tissue Schenck says that there may be increased illumination in air cysts during forced inspiration He also states that emphysematous bullae may be differentiated in that they show no delimiting wall Pneumothorax shows no wall, and in addition to this is outside the lung parenchyma The wall of the tuberculous cavity is thickened, and there is usually some tuberculous infiltration about it The expansile cyst tends to obliterate the lung markings, and at times the findings are not unlike complete pneumothorax There is often some haziness of the lungs at the apices, and the costophrenic angles may be obliterated These last findings are due to the atelectasis of the compressed pulmonary tissue One will notice in the present case report that the obliteration of the costophrenic angles was reported by the roentgenologist as due to fluid

Mortality is high in children and infants Infection is a grave complication, especially in the fluid cyst It has been noted by numerous observers, however, that the condition may be present for many years without producing any symptoms The case being reported is an example of this The prognosis in this case was, of course, bad, and it would seem to be due mainly to two factors first, the small amount of lung parenchyma remaining, and second, increased intrapulmonary pressure

The treatment of this condition is often unsatisfactory Cole and Nalls say that treatment is dependent on the size, number, location and type of cysts, the presence or absence of infection, and urgency for relief of symptoms Wood⁹ says that some cases are improved following bronchoscopic aspiration and injection of lipiodol, but he thinks that this treatment

should be limited to infected cysts which are amenable to this type of drainage. Two of his cases had fluid cysts removed surgically. He mentions one case with a large balloon cyst that was treated by thoracotomy and cauterization of the bronchial communication. Following recovery from this operation, the patient lived 10 years, and finally died of some unrelated condition. Schenck advocates extirpation of the cysts, saying that at times lobectomy should be resorted to, but he adds that the procedure is attended with grave danger. Freedman says that no giant air cyst should be tapped unless it interferes with respiration, because this procedure may be followed by shock and death, but it is often necessary to do emergency thoracenteses in these cases to relieve the pressure. According to King and Harris, Adams emphasizes the importance of attaching to the thoracentesis needle a rubber tube and placing its end under water, thus maintaining equalized intrathoracic pressure. They also state that iodized oil should be injected into the cyst at the first thoracentesis. Pearson¹² says that Adams caused stenosis of bronchi in man by applying 35 per cent silver nitrate through a bronchoscope to the bronchial mucosa. Adams has also suggested injecting silver nitrate into the cysts in an effort to destroy the lining epithelium and thus give better opportunity for obliteration of the cavity. Adams also advised using the thoroscope or straight cystoscope in order to visualize and cauterize the bronchial communication. Naturally, if enough lung units are destroyed, there is no surgical or medical procedure which will do any good.

COMMENT

Our patient was quite uncomfortable, in fact, life was almost unendurable. For this reason, it was decided to try to do something for him surgically. The record shows how unsuccessful we were in this endeavor. It was hoped in the first place to confirm the roentgenologic diagnosis of lung cysts, and in the second place, it was hoped that the opening of the cysts might gradually be blocked by lipiodol, or by nitrate of silver.

From a roentgenologic point of view, this case was typical of that group which has been diagnosed congenital cystic disease of the lungs. But, as Koontz has very correctly said, it is almost impossible to differentiate between congenital cystic disease of the lungs and the acquired form, and in this case we were left in some doubt even at the autopsy table. As will be remembered, lack of pigment is one of the main differential points. In this particular case, there were no fluid cysts, so all the cysts contained air, and naturally contained pigment. Although many of these cysts were on the periphery of the lungs and definitely seemed to be emphysematous bullae, some of them were in the lung tissue. Here, therefore, we have occurring in the lung of the same patient, cysts and emphysematous bullae-like cysts. The roentgenogram of part of the right lung which had been taken in 1932 shows the upper portion of the right lung to be fairly clear except for a few cysts. This piece of evidence would suggest that the cystic condition of

this patient's lung is an acquired one. Although it is impossible to make a definite diagnosis of the etiology, it is certainly logical to suppose that there must have been some fundamental anatomical basis for the cystic disease.

One cannot be sure that all the points mentioned in the pathological report are of diagnostic value. According to this report, the fact that this man had been free of symptoms for 30 years is against there being any pulmonary malformation prior to this time. But various authors state that cases of so-called congenital cystic disease of the lungs may remain symptom-free for years. It would seem, however, that there is a gradual trend to class more and more of these cases as acquired cystic disease rather than as congenital cystic disease of the lung. Pierce and Dirkse¹⁸ say that the term "congenital" is improper in a roentgen diagnosis of cystic pulmonary disease without film evidence of such a lesion at birth.

CONCLUSION

It has been our purpose, first, to report another case of cystic disease of the lungs, secondly, to emphasize the difficulty of differentiating congenital from acquired cystic disease of the lung, and thirdly, to emphasize the difficulty of doing anything mechanically for this type of case, because any reduction in the vital capacity means the difference between life and death.

We are indebted to Duke University Medical School and Hospital for the pathological transcripts and pictures.

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TULAREMIA WITH PULMONARY COMPLICATIONS^{*}

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CREDIT for the first clinical description of tularemia is due to R A Pearce, a country practitioner of Brigham City, Utah, although only a single reference to his work has been found in subsequent reports of this disease. At the annual meeting of the Utah State Medical Society in Salt Lake City, October 3, 1910, he described six cases which he had observed during 1908, and he stated that he had seen 10 others during 1910. An autopsy on the one fatal case was reported as showing a septic meningitis secondary to a horse fly bite on the face.

The following is an excerpt from his article²

"I will give you the histories of a few cases of an infection probably caused by the bite of a large black and yellow horse fly (sometimes called deer fly) all the cases of which, so far as I know, have been distributed over a definite area about Brigham City. This disease made its appearance in August 1908 and August 1910. The point of infection in all my cases has been on the exposed portion of the body. All the cases give a history of having been bitten by the large black horse fly. Most of the patients say they have been bitten by the same flies many times before during that season.

"The incubation period varies from two to five days.

"In all the cases there has been marked swelling of the glands and lymphatics about the area of the bite. In about one half of the cases some of the glands have gone on to suppuration. Most of the cases have had chills some time during the incubation period, others have chilly sensations. The temperatures have run from 98 to 104° F. The duration of the disease has been from one to four weeks, the severity of the disease varying from slight malaise to death.

"All the bites have gone on from a red infiltration like a mosquito bite to complete breaking down of the tissues and sloughing, forming a punched out circular ulcer about one fourth inch in diameter and an eighth inch in depth. Within a few hours of the bite there forms a water blister at the apex of the infiltration, this soon changing to pus and then the tissue begins to slough away, the discharge being like a seropurulent mucus."

Some important early observations were also made by T B Beatty, of the Utah State Board of Health. In 1911 he observed a fatal epidemic among the rabbits in the vicinity of his farm not far from Brigham City, and associated this with an infection of one of his farm hands, resulting from a deer fly bite. As he was unable to obtain cultures from either the

^{*} Read at the Cleveland meeting of the American College of Physicians, April 5, 1940

rabbits or the patient he sought help from the U S Public Health Service. Subsequently, in 1919, Francis identified the disease and the bacterium as identical with the one described by McCoy in 1912.³

No pulmonary complications are recorded among the cases observed at the Latter Day Saints Hospital during the first 10 years after the disease was recognized in Utah. The mortality rate in Utah has been very low for tularemia. In 1938 there were 73 cases reported and only one death, in 1939, 44 cases with three deaths. Unfortunately, there was no autopsy report in any of these fatal cases, and pneumonia is not listed as a complication. Of the last 12 cases in the Latter Day Saints Hospital, five have had pulmonary complications. Since only the very sick patients come to the hospital, this proportion of pulmonary complications is undoubtedly higher than occurs in all the cases treated in the home and the hospitals. All four cases that came to our own service in 1938 and 1939 showed pulmonary complications consisting of bronchitis in one, pleurisy with effusion in three, lung abscess with bronchial fistula and spontaneous pneumothorax in one, a unilateral consolidation followed by pleural effusion in one. One of the cases with pleurisy with effusion developed a moderately severe fibrosis and bronchiectasis in one lower lobe.

The diagnosis was made from the history and a positive agglutination test for tularemia. *Pasturella tularensis* was not recovered from the blood or the pleural effusion in any case.

Most of the cases that have occurred in Utah have had contact with rabbits, some have been bitten by wood ticks and deer flies. Unfortunately, many of the rodents and even the sage hens have been known to harbor the infection.

Three of the four cases with pulmonary complications which I am reporting were sheep shearers. Two of them were not aware of any insect bite and had not handled rabbits, this may suggest inhalation as a possible mode of entry.

All four of these cases were treated with sulfanilamide from 60 to 90 grains a day. Additional therapy consisted of transfusions in two cases and convalescent serum in one. All the cases made complete recovery. Two were desperately sick, and for a time it did not seem possible for them to recover. Foshay's serum was not used, partly because it was not immediately available and because we were anxious to test the therapeutic value of sulfanilamide in desperately sick cases. The rapid improvement in the three cases who were able to tolerate the drug well made us feel that it was definitely of specific value.

A brief summary of the essential facts in the four cases is as follows:

Case 1 A B, male, aged 34, sheep shearer, reported having removed many wood ticks daily from his body and had also dressed a wild rabbit several days before onset. His illness began on May 2, 1938, with a severe backache. On May 5, 1938, he became acutely ill with generalized aches and pains, sweats, fever and pleural pain in his left

chest. These symptoms lasted three weeks. He gradually improved and was up and about for one week. About June 1, 1938, he became acutely ill again with fever, severe cough and pain in his left chest. He remained very sick all through June. About June 22 he felt something break in his chest, and he estimated that he coughed up about one quart of foul sputum in two days. On June 29 he was brought to the Latter Day Saints Hospital. Examination revealed evidence of a pyopneumothorax in the left chest with abscess in the left lower lobe which had undoubtedly opened into a bronchus. He had lost 63 pounds and looked very sick, thin and dehydrated.

Laboratory findings showed Hemoglobin 78 per cent, red blood cells 4,240,000, white blood cells 16,200 with 70 per cent polymorphonuclears. Agglutination test was strongly positive for *B. tularensis*.

Treatment consisted of forced feedings and postural drainage without appreciable change in temperature which ranged from 99 to 102.2° F.

July 1 Sulfanilamide was started in 10 grain doses every four hours.

July 3 Temperature reached normal for the first time and did not exceed 100° F in the next 10 days. During the following 10 days it barely reached 99°. He was given two transfusions, additional artificial pneumothorax and postural drainage.

July 31 He was discharged much improved.

August 11, 1938 He had gained 19 pounds, abscess in lung was rapidly healing, and he was feeling almost well.

September 26, 1939 Further observation showed him to be apparently cured. Roentgen-ray revealed some thickened pleura and limitation of excursion of outer part of left diaphragm but otherwise essentially normal. He had been working for a month.

Case 2 C H, male, aged 37, farmer

June, 1938, he was bitten by a wood tick. This was followed in a few days by a sickness of three weeks' duration consisting of chills, fever, sore throat, general aches and pains. He gradually improved but had recurrent attacks of sore throat and cough all summer.

In September he had an attack of chills, fever, cough and pain in his right chest and a desquamating eruption on his hands.

November 28, 1938, he came to the Clinic complaining of cough with copious sputum, weakness, and loss of weight. He had not been well since his attack in September. Examination revealed fluid in his right pleural cavity, thickened pleura, and many râles. Paracentesis was done, and a straw colored clear fluid was obtained which yielded a sterile culture. It and the sputum were negative for tubercle bacilli. Agglutination for tularemia was strongly positive. He was given sulfanilamide, 40 grains to 60 grains daily, for most of two weeks. The temperature came to normal rapidly and it remained normal. He gained 15 pounds in two weeks. He reported in February that he had continued well since his last examination in December.

Case 3 F S, male, aged 24, sheep shearer. He often found ticks on his body but was not aware of any bites and had not handled any rabbits or rodents. Two weeks before admission to the hospital on June 28, 1938, he became sick with chills, fever, general aches and pains, weakness, nausea and vomiting.

Examination revealed several sores on his forearms which he called grease sores. Temperature was 102° F, pulse 100. He had dullness and many coarse râles in both lower lobes and the right middle lobe, but no definite consolidation. Spleen was palpable. Roentgen-ray film showed slight cloudiness of the lower part of both lungs. Agglutination test was strongly positive for tularemia and moderately so for undulant fever. He was kept under observation for two days without medication. His temperature ranged from 101 to 103°.

July 1, sulfanilamide was started in doses of 10 grains every four hours. The highest temperature in the next 24 hours was 101°, and during the following 24 hours

it reached only 99.2°. From that day on it remained normal, and all his symptoms and physical signs disappeared with his fever. He made a rapid recovery.

Case 4 C. O., male, aged 62, sheep shearers. He was not aware of any insect bites and had not had any contact with rabbits or rodents.

June 1, 1939, he became suddenly ill with nausea, vomiting, diarrhea, chills and fever, general aches and pains and these symptoms continued with increasing severity until he entered the hospital on June 6, 1939. He appeared very sick, dehydrated and delirious. The temperature was 103° F, pulse 90. He had a severe cough. Examination revealed moderate cyanosis and dyspnea, dullness in left lower chest with diminished respiratory murmur and many râles. The following day there was definite consolidation in his left lower lobe. He was deeply intoxicated and continuously delirious. Cyanosis and dyspnea increased. All the agglutination tests were negative until June 19 when he showed positive agglutination for tularemia. His leukocytes ranged from 6200 to 10,900. His course was a very stormy one and on several occasions his prospects seemed almost nil. After the consolidation cleared, he developed fluid in the pleural cavity which was aspirated on July 3 and 10. A clear straw colored fluid, in amounts of 1000 cc and 425 cc, respectively, was removed. Culture from this fluid remained sterile.

His therapy consisted of sulfanilamide whenever he could tolerate it, forced feedings by nasal tube, intravenous glucose, transfusions and injections of convalescent serum from a man who had recently recovered from tularemia. Recovery was slow but complete. Just what part of his therapy deserved most credit for his recovery it was impossible to tell.

COMMENT

Clinical cases of tularemia have been known to exist in Utah since 1908. Most of the earlier cases were of the ulceroglandular type.

Pulmonary complications are either more frequent in recent years or they are more often recognized.

It is possible to acquire the disease by handling infected wild rabbits, many other rodents and some of the larger animals. Unfortunately the disease has also been found in the sage hen and the quail.

Next to the handling of infected rabbits the commonest source of the disease is through the bites of wood ticks and deer or horse flies.

The frequency of the infection with pulmonary complications in sheep shearers who have not, to their knowledge, been exposed to the usual source of infection suggests the possibility of inhalation as the mode of infection.

The mere fact that all of our cases with pulmonary complications recovered after receiving sulfanilamide does not prove it to be a specific. The complications may have been owing to a secondary infection, but such organisms should have been easily recovered in the cultures made. The mortality rate in all cases of tularemia is low, but at least half the cases that die have pulmonary complications. The favorable response to sulfanilamide was so immediate and the patients had been sick so long that it precludes the possibility that the results were just a coincidence.

Our conclusions were that the drug has definite therapeutic value in tularemia.

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CHRONIC ULCERATIVE COLITIS—ALLERGY IN ITS ETIOLOGY *

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THE possibility that chronic ulcerative colitis is the most severe result of colonic allergy should receive serious consideration. In the literature,¹ many instances of colonic allergy are reported. Simple colitis associated with varying degrees of diarrhea, abdominal soreness, cramping, tenesmus and mucus frequently is due to specific food allergies. Wheat, egg, milk, fish, honey, various vegetables, fruits and other foods and condiments have been incriminated. Milk allergy, especially, is a common cause of colitis. Two of my patients who had allergic colitis from milk required only a few teaspoonfuls of milk as a laxative. Friedenwald² studied a patient with diarrhea of six months' duration due to milk allergy, in whom hydrochloric acid by mouth given because of achylia had failed to bring relief. Cardon³ recently reported five cases of colitis with varying degrees of cramping, tenesmus, abdominal soreness and diarrhea due to milk allergy. It is generally agreed that the colic of infancy and other gastrointestinal symptoms of childhood may be due to allergy. In mucous colitis and in the unstable or irritable colon, allergy is so likely to occur that it should always be considered as one of the possible causes. The obvious psychoneurotic tendencies in allergic patients may be due to frustration because of the long-standing unrelieved symptoms or to actual cerebral or nervous tissue allergy.⁴ Gastrointestinal allergy also may result in symptoms and findings suggestive of appendiceal or gall-bladder disease, of acute or chronic intestinal or colonic obstruction and of organic disease of sigmoid and rectum. Local passive transfer in the rectal mucosa in man has been reported by Gray and Walzer,⁵ and of the stomach, small and large intestine, peritoneum, spleen and uterus in the rhesus monkey, by Walzer, Gray, Strauss and Livingston.⁶ Pruritus and sometimes is a mucosal inflammation with cutaneous dermatitis arising from allergy.

These colonic symptoms arising from allergy differ in variety and degree because of allergic reactivity. Varying amounts of allergic mucosal inflammation with serous or mucoid secretion, and generalized mild or severe localized edema, the latter causing signs of obstruction, may occur. Increased vascular permeability is frequent, causing easy bleeding of the mucosa and at times frank hemorrhage, as recently reported by Rubin⁷ in infants with colic. Smooth muscle spasm, which frequently is the result of allergy, may also occur accompanied by cramping, pain and tenesmus.

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In chronic ulcerative colitis, the foregoing allergic reactions may explain the presence of erythema, of the granular type of mucosal inflammation with varying capillary bleeding, and of serous or mucoid secretion. Andresen⁴ is of the same opinion. Such tissue reactions may be similar to those responsible for atopic dermatitis which is characterized by cutaneous erythema, minute papulo-vesicular lesions, thickening, exfoliation, oozing and crusting with secondary infection in varying degrees. Ulceration, denudation of the mucosa, and infection of the colonic tissues may be absent or they may be so severe that septicemia or perforation of the bowel results. Two explanations of the origin of ulcerations are offered. First, if a superimposed infection from colonic bacteria, especially streptococcus, arises, localized ulcerations may develop and produce cellulitis, fever, purulent discharge and subsequent formation of scar tissue, fibrosis and contraction of tissues. Ulcers may vary from the superficial mucosal to the deeper, larger, more penetrating type depending on the patient's resistance to the infection. Second, the ulcerations may arise from localized vascular allergy as do canker sores in the mouth, which allergists agree are usually due to food and less often to drug and bacterial allergy. Similar canker-like recurrent ulcers due to food allergy have been observed in the vulva and vagina of one of my patients. The rôle of allergy in the etiology of peptic and corneal ulcers has long received consideration in the literature.¹ Also the tendency to polyp formation suggests allergy as the cause. Practically all the polyps that arise in the nasosinal mucosa are due to allergy, and polyposis in the stomach has occurred in some definitely allergic patients.

Thus, chronic ulcerative colitis in all its stages may be caused primarily by allergy and secondarily by superimposed infection and the effects of resultant avitaminosis.

In cases in which food allergy is the cause, the tissue reactions may arise from blood-borne allergens absorbed from the stomach or small intestine or from food allergens absorbed from the colonic content itself which might produce a contact-like reaction. The latter is possible because of the rapidity with which ingested foods, usually inadequately digested, reach the colon in cases of diarrhea.

Furthermore, the recognized characteristics of clinical allergy may explain some of the characteristics and variations of chronic ulcerative colitis.¹ Allergic reactions are localized in various tissues. Thus, alimentary allergy may be present only in the mouth, in the stomach, in part of the small intestine, in the cecum, in the sigmoid or rectum, or in restricted or large areas of the colon. After it has been established, it tends to extend to larger areas. Regional enteritis, especially in the ileum, should be studied from the allergic point of view. The recurrent attacks of asthma, migraine or urticaria frequently may result from refractoriness or hyposensitization of the shock tissues. Anergy or² failure of tissues to react allergically also may occur. These observations may explain why remissions and variations in symptoms arise in certain patients with chronic ulcerative colitis.³ The re-

ported beneficial effects on food allergy of the summer months and of residence away from the ocean,¹⁰ especially in dry inland areas, also may explain some of the variations in colonic symptoms. Other environmental and seasonal influences have been observed especially in inhalant allergies (Case 2)

CLINICAL STUDIES

Andresen⁸ first reported food allergy as a cause of ulcerative colitis*. One patient had a return of bloody, mucoid dysentery from eight drops of milk concealed in his food the night before.

Hare,¹¹ in 1935, found that 85 per cent of 38 patients with chronic ulcerative colitis had definite family or personal histories of allergy. She noted its occurrence in adolescents and young adults, especially in females, and its precipitation by acute infection.

Mackie,¹² in 1938, maintained that the relation of chronic ulcerative colitis to allergy, particularly to food allergy, requires study. Since skin tests failed to demonstrate clinical sensitizations to food in most instances modified elimination diets of the writer were used to study possible food allergy. Of 67 cases thus studied, definite indications of food allergy were noted in 44 and equivocal evidence in seven. Milk, egg, orange, wheat, spinach, and tomato named in the order of frequency, headed the list of allergenic foods. Evidence of bacterial allergy also was noted. Mackie emphasized the frequency of avitaminosis, hypoproteinemia, and loss of weight owing to improper utilization of ingested foods.

PERSONAL STUDIES

Cases 1 and 2 In December of 1937, two patients reported because of perennial nasal allergy and looseness of the bowels. One of these, a woman aged 35, had suffered from nasal and bowel symptoms all her life. Diagnosis of ulcerative colitis had been made. The possibility of infectious and parasitical colitis had been investigated and psychoneurosis had been considered. With fruit-free elimination diets her nasal symptoms and the looseness of bowels had been entirely controlled for the last three years. Milk in small amounts rapidly caused nasal congestion and diarrhea.

The other, a man, aged 29, had had similar nasal and bowel symptoms for 14 years. He had had bronchial asthma all his life, although it had improved the last 10 years. A brother had asthma and a sister had colitis. As amebae had been found on one occasion the patient had been treated with anti-amebic drugs. Colonic irrigations, and injections of thiamin and liver had been used. Diagnosis of ulcerative colitis had been made by roentgen-ray and by repeated proctoscopic examinations. During the past three years, on a diet eliminating milk and several fruits and vegetables, the colitis improved definitely. We believe that better results would be obtained if the patient adhered more strictly to the diet. Because of his positive skin reactions and the seasonal exaggeration of his nasal allergy, pollen therapy also was administered.

Case 3 In September of 1938, a man, aged 28, who had chronic ulcerative colitis of four months' duration was first seen at the Alameda County Hospital. He had had loose stools, up to 20 a day, with varying amounts of blood, mucus and pus as well as

* Since acceptance of this article, Andresen has published *Ulcerative colitis—an allergic phenomenon*, *Am Jr Digest Dis*, 1942, ix, 91.

frequent incontinence. His temperature varied from 99° to 102° F., and his weight and strength were markedly impaired. Diagnosis had been made by proctoscopic and roentgen-ray studies. The patient had always disliked milk. No other indications of allergy were noted. This was his first illness. Skin reactions to all ingested and inhaled allergens by the scratch test were negative. Stool examinations for parasites and cultures for bacillary dysentery were negative. Therapy with emetine for 14 days and with liver extract and thiamin every three days for two weeks hypodermically had failed to help. Metaphen by vein had been given for two weeks.

On a fruit-free and cereal-free elimination diet in soft, liquid, minced or pureed form, the bowel movements were reduced, within two weeks, to four to six in 24 hours, and the blood and mucus in the stools were reduced. One month later the patient had only two to three formed stools daily. In the last two years, he has had one to two formed stools in 24 hours, entirely free of blood and mucus. Proctoscopic examinations at frequent intervals revealed no ulcers or mucosal inflammation for the last two years. In May 1939, the patient ate a small piece of chocolate cake, within four hours looseness of bowels developed which persisted for 24 hours. Grapefruit, lemon, cooked pears, peaches, apricots and eggs were added to his diet. Because of the possible history of milk allergy and because of the importance of preventing a return of the colitis, milk was not given. At the last observation the patient felt well. In the last three years he did not lose a day's work in a steel mill because of illness. He weighed 50 pounds more than when he was first seen.

We believe that food allergy, especially to milk and probably to wheat, was the major cause of the ulcerative colitis in this case. The rapid improvement during the first month of dieting, the long-standing dislike for milk and the definite diarrhea after eating cake confirm this assumption. Furthermore, we believe that the injections of thiamin and liver extract (as suggested by Cheney¹³), for 10 months, two to three times a week after the patient left the hospital, relieved probable avitaminosis, and that neoprontosil by mouth (as suggested by Brown, Herrell and Barger¹⁴) in two courses, in the first six months after hospitalization, may have discouraged persisting secondary infection. No medication had been given for two years prior to the last observation. The bowel was then normal by proctoscopic and roentgen-ray examinations.

Case 4 A man, aged 32, observed in the Medical Clinic of the University of California Hospital, had been suffering from chronic ulcerative colitis for five years. Proctoscopic examination revealed a red, glistening mucosa with adherent mucus and many small ulcerations. The roentgen-ray showed absence of haustra in a narrowed descending colon. Watery movements, at times streaked with blood and containing mucus, had numbered 12 to 20 a day for several years. Loss of weight and strength was marked. No cause had been found for the diarrhea after careful laboratory tests of all types. The patient was placed on a cereal-free and fruit-free elimination diet, all the foods were cooked, pureed or minced. In two weeks the diarrhea had decreased. Since then (in two and a half years) the stools declined to two to four a day, they usually were semi-formed. The patient gained 18 pounds in weight, and his strength and energy returned. At last observation he was eating beef, lamb, liver, tongue, chicken, white and sweet potato, most of the vegetables (still cooked but no longer pureed), pears, peaches, tapioca, sugar, sesame oil and salt. He received daily 50 mg. ascorbic acid by mouth. Tea and soy-lima bread produced diarrhea. Other foods commonly productive of allergy had not been tried in his case.

Case 5 A man, aged 61, developed diarrhea in late September, 1940. The next day watery, bloody movements with severe tenesmus and a fever up to 102° F. were present. Agglutination tests on the blood serum, stool cultures, and microscopic examination of the stools offered no explanation for the diarrhea. Finally a roentgen-

ray picture of the barium filled colon showed typical ulcerations in the sigmoid and parts of the ascending and transverse colons. Proctoscopic examination showed superficial ulcerations and a congested, easily bleeding mucosa with some adherent bloody mucus. Microscopic examination of a piece of the rectal mucosa showed many eosinophiles. The personal and family history of allergy was negative. There was no history of any idiosyncrasy or dislike for foods. Skin reactions with the scratch test to food allergens were negative.

A diagnosis of acute ulcerative colitis was made and a cereal-free and fruit-free elimination diet was prescribed. All foods were cooked, pureed, or minced and given in small amounts at frequent intervals. Immediately stools reduced in number.



FIG 1



FIG 2

FIGS 1 and 2 Roentgen-ray pictures of the colon of Case 5. The typical ulcerations in the sigmoid and transverse colon are shown in figure 1. The normal colon four months after the elimination diet was instituted is shown in figure 2.

In four or five days only three or four stools devoid of blood and mucus were passed, and in 10 days his normal bowel activity had returned. Rice, corn, rye, eggs, fish, fresh grapefruit and lemon, cooked pears, peaches, apricots and prunes were gradually added, and in the last six months all other foods were tried. Each time milk was taken cramping and diarrhea developed in a few hours. His colon was normal by proctoscopic and roentgen-ray examinations.

Case 6 A woman, aged 31, was seen in January 1941 with a history of chronic ulcerative colitis of six years' duration. Liquid to soft stools, varying from six to 20 daily, with intermittent blood and mucus, cramping, tenesmus and abdominal soreness and moderate fever had been present since 1935. Much abdominal soreness and pain, especially in the right side, had occurred. Weight had fallen 50 pounds. Fatigue and somnolence had been present for four years before colitis had developed. The mother had had sick headaches for years, and the patient had frequent nasal congestion.

Proctoscopic and roentgen-ray examinations had indicated chronic ulcerative colitis. Treatment with bland diets, oral vitamins, tincture of opium, liver and iron injections, autogenous stool and Barger's vaccines had been of no benefit.

Moderate nasal congestion suggested possible allergy. The patient had been susceptible to prolonged head colds with fever since her teens. Her dietary history revealed no food dislikes or disagreements, except that crab produced diarrhea. Alcoholic beverages and tobacco smoke produced cramping and diarrhea. Skin reactions by the scratch tests with all important foods and inhalants were negative.

The patient was placed on a cereal-free and fruit-free elimination diet, consisting of soft, pureed, liquid or minced foods. Within one month she had two to three formed stools every 24 hours and was free of urgency and incontinence. At the last observation she had one or two formed stools daily. All abdominal and bowel symptoms were gone. Constipation might occur. Her strength, energy and appetite increased. For the first time in 10 years she was doing her own work.

She received by mouth synthetic vitamin C, thiamin, riboflavin, pantothenic and nicotinic acids, viosterol, and calcium carbonate. Repeated trials showed that corn, sweet potato, tomato, onion and peaches caused diarrhea. Eggs were tolerated. Milk and wheat were not tried because of the excellent results obtained and because of my desire to prevent any marked allergic reaction in the colon.

Case 7 A man 22 years of age developed intermittent cramping and diarrhea in 1938. During the following year, these symptoms increased in degree and frequency and blood often was noted in the stools. In 1940 he had loose stools six to 10 times every 24 hours with blood, at times in large amounts. Fatigue, weakness and nervousness were marked. No treatment was given except retention enemas and local rectal applications. On a soft smooth diet with extra milk, his symptoms steadily increased.

We first saw this patient in the Medical Clinic of the University of California Hospital. Roentgen-ray and proctoscopic examinations showed definite ulcerative colitis. Stool examinations for parasites were negative. He had had no colic or feeding disturbances in childhood, but had been troubled with constipation all his life for which he had often taken laxatives. He had had recurrent bronchitis from the fall to the spring months up to the age of 17. One attack of asthma occurred five years previously. Moderate nasal congestion and "catarrh" had been present for years. His father had had constipation and distention for many years and rheumatic pains and soreness for 10 years. The patient gave no history of food idiosyncrasies or dislikes.

In January 1941, he was placed on a fruit-free and cereal-free elimination diet in soft, minced or liquid form. In three weeks he had only three soft, semi-formed stools without blood in 24 hours. Since then he had one or two formed stools in 24 hours without cramping, abdominal soreness or blood. He gained 15 pounds in spite of constant hard work, and his weakness, fatigue and nervousness entirely disappeared. He reacted to milk with definite diarrhea and cramping. He tolerated eggs. His reaction to wheat was in question.

Case 8 A man aged 38 had had frequent loose stools and cramping, with blood and mucus, for four years. Beginning in June 1939 he had two to three watery movements daily with an increased amount of blood and mucus. Proctoscopic examination showed an inflamed mucosa with many small irregular superficial ulcers. During the following seven months he was in three different hospitals. Therapy consisted of three transfusions, administration of vitamin and of liver, and other dietary and medical treatment. An ischio-rectal abscess and anal fistula developed. Fever and continual bloody diarrhea persisted. Gradually the patient improved and in May 1940 he returned to work. However, easy fatigue, weakness, abdominal soreness, cramping and bowel urgency, with four to six semi-watery stools, persisted.

In March 1941 these symptoms increased and the patient entered Highland Hospital on May 30. Proctoscopic and roentgen-ray studies showed a reactivated chronic ulcerative colitis from the hepatic flexure to the sigmoid. The patient had a temperature up to 101° F, watery stools up to 16 per day with much incontinence, blood, pus and mucus, and loss of weight, strength and appetite. Sulfanilamide and later sulfaguanidine, thiamin and liver given parenterally and two transfusions produced no definite benefit.

On July 17 a cereal-free and fruit-free elimination diet, consisting of soft, liquid, minced or pureed foods, was instituted. In three weeks the patient had only one to two semi-formed stools with no blood or mucus each 24 hours. The fever disappeared, and appetite and strength increased. Since then formed stools continued, the patient's weight increased 34 pounds, and he was at work on an automobile assembly line for three months. His strength and health were better than in six years. Recent proctoscopic examination by Dr P J Dick showed extensive plaque-like healed scars several centimeters long. The adjacent mucosa in places was edematous, but no polypi, bleeding, oozing or ulcerations of the mucosa or decrease in the size of the intestinal lumen were seen.

This patient's family and personal histories of allergy were negative. Scratch tests with foods were negative. There was no history of food dislikes or idiosyncrasies.

Case 9 A boy eight and a half years of age had passed blood-streaked stools every few months since May 1938. Before entering the Children's Hospital in Oakland in August 1941, he had passed loose or liquid stools with increasing amounts of blood and mucus three to six times each 24 hours for eight months. Urgency and incontinence often had kept him out of school. For three years increasing fatigue, irritability, loss of appetite and recently afternoon temperature up to 102.5° F had been present. Physical examination was negative except for a scaling and thickening of the skin around the mouth, a facial tic, and diffuse moderate soreness of the abdomen on palpation. Blood and urine analyses were normal. Stool examinations showed much blood, pus and mucus but no parasites. Stool cultures and serum agglutinations were negative for bacterial causes of dysentery. Proctoscopic examination showed an edematous, granular mucosa with mucopurulent discharge. Roentgen-ray studies of the colon showed poorly developed haustrations in the descending colon and sigmoid, and a diffuse fine irregularity of the mucosa.

A fruit-free and cereal-free elimination diet in soft, liquid, minced or pureed form was started on September 9. Blood and mucus disappeared in a week. In two weeks the patient passed a soft or semi-formed stool only every one to three days. Within one month the stools became formed. On September 16, because of continued afternoon fever, sulfathiazole was given in doses of 60 grs daily for one week, followed by 40 grs daily for nine days. The temperature became normal in three days, remained normal for nine days, but again rose to 101° or 102° F during the last four days of administration of this drug. Since the fever continued for five days, sulfaguanidine in doses of 60 grs daily for one week and 40 grs for two weeks was given. The temperature remained below 100° F by rectum after October 13. Since mucosal infection was assumed to be the cause of the fever, increasing doses of Barden's streptococcal vaccine and of stock respiratory organisms were administered at first every two to three days and then every five to seven days.

For the last three months the bowels were normal with no blood or mucus, appetite, strength and energy increased, no fever was present, and the facial tic and dermatitis around the mouth disappeared. The patient gained 12 pounds in weight. Rice, corn and rye, egg, pear, peach, apricot and celery were added to his original diet. His foods were cooked in the usual manner without pureeing or mincing. He was taking one teaspoonful of calcium carbonate a day and viosterol in sesame oil, 10 drops daily. Recent proctoscopic examination revealed a slightly granular mucosa but no ulcerations or points of bleeding.

Case 10. A man, aged 25 years, had had diarrhea with blood and cramping for two weeks in July 1935. The cramping recurred for one to two hours for one to two days every one to three weeks until July 1936. At that time severe, bloody diarrhea with fever set in, apparently after ingestion of strawberries. The patient was in the hospital for 24 days. Milk disagreed with him. From November until May 1937 he had four to six loose stools daily with occasional blood. The symptoms continued in varying degree until July 1940 when after drinking much loganberry juice, his most severe bloody diarrhea with mucus and cramping developed. Sulfanilamide gave no relief. Upon diet trial ordered by Dr. J. E. Hunter of Seattle the colitis has definitely improved. In order of harmfulness the following foods have been incriminated: nuts, berries, pepper, cabbage, cauliflower, corn, beer, coarse bread and vegetables, sweet potato, alcohol in excess, raw fruits and vegetables, and milk. The patient had known that potato and milk caused "gas." He had had no allergic diseases in the past except occasional hives. His family history revealed that his mother had hay fever and "sick" headaches. A maternal aunt and grandmother had had "sick" headaches. The father had had boils on his face after eating pork.

In October 1940, Dr. T. T. Mackie informed me of a case of seasonal ulcerative colitis recurring each year during the ragweed season. Marked relief occurred in an air conditioned room, and a severe exaggeration of the colitis resulted from the hypodermic administration of ragweed pollen. A similar case studied in the last 14 months follows and is the first published record of complete relief from pollen therapy.

Case 11. A woman aged 43 who was seen in the Clinic of the University of California Hospital in September 1940, had had chronic seasonal ulcerative colitis since 1931. Watery or loose stools with blood and mucus associated with moderate fever varying in degrees, weakness, malaise and dull or cramping pains in the lower abdomen recurred each year during July or August and lasted until November or December. She had been first seen in the clinic in September 1934. At that time a proctoscopic examination had revealed a granular and hyperemic mucosa with many small ulcerations and bleeding areas. Since then other proctoscopic examinations during the autumn months had confirmed the diagnosis of "idiopathic" ulcerative colitis. Stool examinations for parasites had been negative. Stool cultures in 1936 had yielded hemolytic *Bacillus coli*, *Staphylococcus aureus* and alpha hemolytic streptococcus from which vaccine, lysate and bacteriophage were made. The vaccine given subcutaneously, the phage by mouth, and the lysate applied to the rectal mucosa, had yielded no definite results.

As a child the patient had had croup. "Sick" headaches had recurred for many years especially during menstrual periods. Mild hay fever in the fall had recurred from 1918 to 1923 in Chicago. Her dietary history was negative except that for years eggs had caused belching. Her family history was unknown.

In September 1940, she was tested by the scratch and intradermal methods with all inhalants including all important pollens of this area. Negative reactions resulted except for a one-plus reaction to Red top and Curly dock pollens. However, because of the seasonal recurrence of her colitis, an antigen containing ray, bermuda, mugwort, coastal sage, rough pigweed, white goosefoot, false ragweed, Russian thistle and pickle weed pollens was prepared and administered from the fall of 1940 until the time of this report. For the first time in 11 years no symptoms whatsoever developed in the fall of 1941. Her blood counts were as follows:

	9/28/40	1/28/41	4/29/41
White blood cells	15,050	10,500	11,600
Eosinophilic neutrophils	22%	6%	1%

PATIENTS UNCONTROLLED THROUGH ALLERGIC STUDY

During the last two and one half years four patients with chronic ulcerative colitis have failed to respond to elimination diets

Case 12 A woman 34 years of age entered the University of California Hospital on March 31, 1939. Cramping and diarrhea, with some blood, had first occurred for one week in August, 1938. By mid-December 10 to 15 watery stools a day with blood, pus and mucus had developed and persisted. Increasing weakness, fatigue, anorexia, anemia and loss of weight had been present. Six weeks previously a chill had occurred and a daily temperature up to 101° to 104° F had continued since then. No parasites or positive agglutinations were demonstrated. Proctoscopic examination showed severe ulcerative colitis. Previous treatment had included intensive administration of vitamins A, B, C and D, emetine and carbazone, high caloric diets, calcium gluconate by vein, five blood transfusions, reticulogen in doses of 1 cc daily for two weeks, sulfanilamide and sulfapyridine by mouth, tincture of opium (for cramps), and Barger's vaccine hypodermically.

On April 13, a cereal-free and fruit-free elimination diet was instituted. In three days the stools were less frequent. However, a rectovaginal fistula had developed three weeks before and the apparent improvement was terminated by perforation of the sigmoid with resultant shock, peritonitis and death two days later. Autopsy revealed acute ulcerative colitis with perforation of the sigmoid, pelvic abscess, rectovaginal fistula, acute ulcerative esophagitis and fatty degeneration of the liver.

Case 13 A man 20 years of age was first seen in the University of California Hospital in September 1940 with chronic ulcerative colitis. Diarrhea with mucus and blood had gradually developed in 1934. Since then bland diets, Barger's and autogenous vaccines, and carbazone had been given. Periods of improvement and prolonged exacerbations had recurred but the symptoms had persisted. Since January 1940, loose stools up to 14 a day, with blood, pus and mucus associated with intermittent fever, had continued. Sulfanilamide by mouth, and thiamin and liver extract parenterally had failed to improve the condition.

On October 22 the patient was placed on a cereal-free and fruit-free elimination diet. In addition thiamin and liver extract intramuscularly, dilute hydrochloric acid with feedings, vitamin C, viosterol and calcium gluconate by mouth were given. In two weeks the patient felt better. The mucus and blood in the stools had diminished, but the diarrhea and fever continued. In spite of other elimination diets his symptoms, especially the fever, persisted, and septicemia was suspected. Blood cultures, however, were negative.

On December 9 Dr. Leon Goldman did an ileostomy, soon after which, on a high caloric diet, the patient's weight and strength increased and the fever disappeared. In spite of this improvement and diversion of the fecal contents through the artificial opening, blood, mucus and pus continued to be passed per rectum. On July 2, 1941, Dr. Goldman did a colectomy. Recovery was rapid. The patient's strength increased, and his weight increased 60 pounds since the first operation.

Case 14 A man, aged 50, who was first seen in the Medical Clinic of the University of California Hospital in July 1941, had had chronic ulcerative colitis for four and one-half years. For the first one and one-half years, five to six soft or watery stools in 24 hours recurred for one to three weeks every one to two months. In the last three years bright blood with some mucus had varied in degree, and recurrent colitis had prevented the patient from working. Various diets and medications had been of no benefit. Proctoscopic examination revealed a red, angry-looking, granular mucosa which bled freely in small areas. A great-aunt had had asthma. The patient had had frequent gastrointestinal upsets with vomiting in childhood.

On July 29, 1941, a cereal-free and fruit-free elimination diet was instituted. In 12 days the patient passed stools less liquid with fewer flecks of blood every two to four hours. In addition to the diet, B vitamins, cevitamic acid and calcium carbonate by mouth and liver extract intramuscularly were given. On August 12, stools had declined to six to eight a day, were soft, and showed only a few traces of blood. The patient felt he was stronger but his appetite remained poor. Because of a moderate anemia, the flecks of blood in the stools, and a slight fever, he was hospitalized.

Neoprontosil and later sulfanilamide by mouth were of no benefit. His weight and appetite decreased, possibly due to the drug therapy. The elimination diet was displaced by a high caloric bland diet. Sulfaguanidine was administered together with thiamin and liver intramuscularly. The patient was discharged from the hospital unimproved and ileostomy with subsequent colectomy was advised.

Case 15 A man 30 years of age had had intermittent rectal bleeding attributed to hemorrhoids in 1936 and 1937. Since then varying degrees of diarrhea with blood, mucus and pus, and a temperature up to 104° F had persisted. Proctoscopic and roentgen-ray studies had revealed chronic ulcerative colitis. Vitamin B and liver extract, vitamins A, B₁, riboflavin, nicotinic acid, vitamin D and yeast had been given in large amounts by mouth. Sulfathiazole, sulfanilamide and sulfaguanidine by mouth, retention enemas of various medications, various diets and vaccine therapy had been of no benefit. An ileostomy had been done eight months previously. Since his bowel symptoms and fever continued, a fruit-free and cereal-free elimination diet was tried for four weeks, at the request of Dr. F. B. Taylor, without evident benefit. Thereafter a colectomy was done which was followed by satisfactory recovery.

A history of infantile eczema in the first year of life, of feeding difficulties, constipation and malnutrition had suggested possible food allergy. Nasal congestion with postnasal mucus had been present for several years. Moreover, the mother had had angioneurotic edema from meat, milk and wheat allergy.

SUGGESTED ALLERGIC STUDY AND TREATMENT

A routine investigation of chronic ulcerative colitis from the allergic point of view is important. For the study of possible food allergy, we have used a modification of the cereal-free and fruit-free elimination diet.¹⁵ When frequent liquid stools are present, the foods should be liquid, soft, pureed or minced. Foods which infrequently cause allergy are included. Fruits are excluded until improvement has occurred. Beef is also excluded at first because of allergens common to beef and milk, the latter food being a frequent offender in this disease. If skin testing is done by the scratch tests and positive reactions to any food are definite or if there is a history of definite idiosyncrasy to any food in the diet, a substitute non-reacting food is used. However, the fallibility of the skin test must be kept in mind. When intolerance or allergy to legumes is evident, rice or additional potato may be used. Protein metabolism should be protected with an adequate intake of prescribed meat or soy bean, the latter being the only vegetable source of all amino acids necessary for human nutrition. Homogenized lamb, as well as beef and liver,* may be combined with pureed vegetables, soy bean or split pea.

* Prepared by Clapp & Co., Rochester, N. Y. Not available until after the war.

The following diet is recommended and may be modified as suggested

CEREAL-FREE AND FRUIT-FREE ELIMINATION DIET

(Liquid, Soft, Pureed or Minced)

Tapioca cooked with sugar, with or without soy bean milk, or with maple syrup or caramelized sugar

White or sweet potato—boiled, baked or riced, served with sesame or soy bean oil and salt

Lamb-chops, roast or tongue, minced or ground at first, cooked with salt but without butter or other seasoning Homogenized lamb may be combined with prescribed vegetables

Soy bean puree—best made from canned cooked beans or from cooked soy bean flour (Split pea puree may also be used)

Carrots, beets, peas, squash, artichokes (fresh cooked or canned), strained or pureed Salt, soy bean or sesame oil may be added but no butter or other ingredients

Breads¹⁵ made of soy, lima, potato or tapioca flours Soy bean butter, carrot preserves or maple syrup may be used in lieu of butter

Soy bean milk (Mull-soy or made by our soy bean milk formula)¹⁵

Soy bean or sesame oil (used as noted above)

Sugar, beet or cane, may be taken in water or in mate (Brazilian tea) or in ordinary tea

Salt

Mate

Tea

Until bowel activity decreases, feedings of moderate size should be given every two hours Meat and soy bean are essential to meet the protein requirements The carbohydrate foods, sugar and oil provide for sufficient calories to maintain the proper weight

Thiamin and other synthetic B vitamins, synthetic A or caritol in sesame oil, synthetic C, and viosterol in sesame oil or Drisdol should be given as required The approximate vitamin content of ingested foods may be determined by certain tables* Hypermotility may prevent vitamin absorption, and, therefore, hypodermic administration, especially of thiamin and cevitic acid, may become necessary in severe cases

The diet should be continued for three to four weeks Even after improvement has occurred it may be continued provided nutrition and weight are protected adequately When improvement is unquestioned, other foods from the elimination diets may be added, one or two at a time, every seven to 14 days as follows beef, bacon, rice, corn, spinach, asparagus, string beans, pears, peach, apricot and grapefruit (Fruits may be tried early) Uncooked vegetables and fruits should be added with caution Foods commonly productive of allergy such as wheat, milk, eggs, fish, orange, apple, banana, berries, the cabbage group, honey and nuts should be given only after marked or complete relief has persisted for several weeks or months

*Most of the recent tables may be obtained from Lela E Booker, United States Department of Agriculture, Bureau of Home Economics, Washington, D C

The necessity of partial or complete exclusion of allergenic foods gradually can be determined by such diet trial. A more detailed discussion of the use and development of the elimination diet is contained in our recent manual.¹⁶

If the original diet has brought about no relief in three or four weeks and food allergy is definitely suspected, other elimination diets may be used for two or three months before food allergy is discarded as a possible cause. It is always possible that colonic allergy to foods in the prescribed elimination diet, or in fact to any food, may exist. Nutrition and weight at all times must be protected.

Chronic allergy, especially to foods, produces changes in cellular structure and function, recovery from which requires long freedom from the causative allergens. Thus, if the symptoms of ulcerative colitis are definitely disappearing, it is a good plan to eliminate those foods which are suspected of possible allergy for weeks provided that satisfactory weight and nutrition are maintained. Anxiety to test out suspected or additional foods may retard or obscure progress which would be continuous with the initial or a slightly enlarged diet.

IMPORTANCE OF RULING OUT OTHER CAUSES OF DIARRHEA

All causes of dysentery or diarrhea must be ruled out by thorough physical examination and indicated laboratory tests before a diagnosis of idiopathic or chronic ulcerative colitis can be made. Bacillary, amebic, and parasitical agents, intestinal tuberculosis, or malignancy, acute bacterial or virus infections, and achylia are chief among the less common causes of diarrhea and dysentery.

CASES SUITABLE FOR ALLERGIC STUDY AND CONTROL

(1) Patients with fulminating ulcerative colitis should be given the elimination diet. Such diet trial is justified especially since in these cases surgical operation is associated with high mortality. Antidiarrheal medications, such as codeine, tincture of opium, bismuth or proteo-tannates, may be used if improvement does not result from these dietary measures in a few days. Codeine or tincture of opium should be discontinued as soon as even slight relief is obtained. It is generally conceded that colonic irrigation with so-called intestinal antiseptics is of no value. Maintenance of weight already has been emphasized. If the diet is effective, the symptoms gradually disappear in one to three weeks, and drugs become unnecessary.

(2) The elimination diets should be tried in early mild cases and in chronic cases, especially if septicemia or threatening perforation is absent. The possibility of benefit from such diet is increased when fever is absent or slight and intermittent, when proctoscopic examination reveals only erythema and granulation or scattered or superficial mucosal ulcerations, and when the blood count and sedimentation rate do not indicate much infection. If food allergy and secondary infection are possible factors in cer-

tain chronic cases, the use of elimination diets together with one of the sulfonamide drugs may be of special benefit. The time necessary for the trial diet and the subsequent addition of food has already been discussed. In these cases avitaminosis, anemia, and hypoproteinemia require proper therapy. Donald and Brown¹⁰ recently have emphasized the importance of adequate protein and vitamin intake, especially vitamin C, until fruits and vegetables are well tolerated. Thiamin by mouth and hypodermically and liver extract parenterally as suggested by Cheney¹³ may be given. Shiffrer and Ferguson,¹⁷ however, have failed to benefit cases of chronic ulcerative colitis with such therapy. Iron by mouth and blood or serum transfusions may be indicated.

(3) Because of the advisability of considering food allergy as a possible cause of non-seasonal chronic ulcerative colitis, the elimination diets should also be tried for three to six weeks in the most severe cases. In these cases weight maintenance and proper attention to avitaminosis, anemia, and hypoproteinemia are imperative. The indications for surgery, as discussed by Cave¹⁸ and Jones¹⁹ must be kept in mind. Although allergy may have been the initial and primary cause of the colitis, the secondary bacterial invasion with resultant cellulitis, the danger of septicemia, and of perforation of ulcerated areas may be such that the control of the allergy itself could exert no influence on the infection or pathologic condition in the colon.²⁰ If surgical treatment seems to be required for ultimate relief, it should be carried out before an emergency arises. The elimination diet or therapy for possible bacterial or inhalant allergy may be desirable during the preoperative and postoperative periods, if the symptoms and the physical condition of the patient are obviously improved thereby. On the other hand, the elimination diet may not be required postoperatively, even if colonic allergy has been the original cause, since the sensitized tissues are either removed through final colectomy or are prevented from contact with the allergenic foods through ileostomy. Indeed, if allergy is the primary cause of ulcerative colitis, surgery offers the possibility to remove the shock tissues themselves—an accomplishment impossible in nasal, bronchial or cutaneous allergy.

DISCUSSION

By use of the elimination diets, complete relief of symptoms was obtained in seven of the 14 cases. The relief in Cases 2, 4 and 10 probably would have been greater if cooperation had been complete. The seasonal history did not indicate diet trial in Case 11. In six of the controlled cases specific foods reproduced diarrhea. Because of the severity of the disease in Case 3, because of the patient's complete relief, his gain of 44 pounds, and his continued ability to work in a steel foundry for three years without illness, no attempt has been made to determine the rôle of wheat and milk up to the present time. However, a piece of cake had brought on diarrhea in two hours. The small amounts of wheat, milk and egg taken

CHART I
Chronic Ulcerative Colitis

Results from Allergic Control																									
Case No	Sex	Age	Previous History						Previous Treatment							Improvement						Foods Incriminated	Allergic History		Skin Reactions
			Years of Disease	Severity	Fever in	Oral Vit B	Parenteral		Sulfonamide	Arsenic Drugs	Emetine	Vaccine	Transfusion	Duration of	Degree of	Weight Gain	Co-operation	Family	Personal						
							Vit B	Liver																	
																				Weeks	Years				
1	F	35	3	2	0							2	4	4	20	4	Milk, egg, chocolate	Asthma, hives	Nasal allergy	Foods, inhalants					
2	M	29	16	4	1	+		+		+	+		2	4	2	6	2	Milk, several fruits, and veg	Asthma, colitis in sister	Asthma, hay fever	Inhalants				
3	M	28	1 1/3	4	3	+	+	+		+	+	+	2	3	4	44	4	Milk?, wheat?, chocolate?	0	0	Neg				
4	M	32	5	3	1	+		+				2	2	3	18	3	Not determined	0	0	Not done					
5	M	61	1 1/2	4	3							4	1 1/4 days	4	10	4	Milk	0	0	Neg					
6	F	31	6	3	1	+	+	+			+	4	5/8	4	-10	4	Corn, peas, peach, onion, sweet pot	Sick, headache	Nasal allergy	Neg					
7	M	22	3	2	0							3	3/4	4	15	4	Milk, wheat?	0	0	Neg					
8	M	38	6	4	3	+	+	+				2	1/3	4	34	4	Not determined	0	0	Not done					

CHART I (Continued)

		Previous Treatment										Results from Allergic Control											
Case No	Sex	Age	Previous History			Oral Vit B	Parenteral		Sulfonamide	Ar-senic Drugs	Emetine	Vaccine	Transfusion	Improvement					Food ¹⁴ Incriminated	Allergic History		Skin Reactions	
			Years of Disease	Severity	Reversion in		Vit B	Liver						On set of Weeks	Duration of Years	Degree of	Weight Gain	Cooperation		Family	Person id		
9	M	8½	3	3	3									1	¼	4	10	4	Not determined	0	0	Not done	
10	M	25	6	3	2			+							1	3	10	3	Nuts, berries, cabbage, sweet pot., milk	Hay fever, sick head-ache	Hives	Not done	
11	F	43	9 Falls only	3	0							+		Pollen therapy for 1 year with complete relief					Unknown	Sick head-ache, hay fever	Neg		
12	F	34	¾	4	4	+	+	+	+	+	+	+		2	0	Death from perforation of ulcerated sigmoid							Not done
13	M	20	6	4	3	+	+	+	+	+	+			None	0	None	15	4	Ileostomy—later colectomy with gain of 60 lbs			Neg	
14	M	50	4½	3	1									2	?	1	0	4	Still under observation	0	Sick head-ache	Not done	
15	M	30	5	3	2	+		+				+		None		Former ileostomy Recent colectomy					Eczema, nasal allergy	Hives	Not done

Degree of severity, fever, improvement and cooperation on basis of 4 0 = None 4 = Maximum

occasionally by the patient in Case 4 may account for the continuance of three to four soft bowel movements a day. His gain of 18 pounds and the return of normal strength and energy indicate that he was satisfactorily controlled. Because of the chronicity of the disease and the complete involvement of the colon as shown by roentgen-ray, as well as the excellent recovery, the effect of milk and wheat in Case 6 has not yet been determined. Loss of weight at first was possibly caused by influenza, by failure to take enough calories in the diet, and by early resumption of activities. Because of the excellent results in Cases 8 and 9, the effects of common allergenic foods have not been tested. The relief by the elimination of specific foods in Case 10 was the result of diet trial elsewhere.

If symptoms return with the ingestion of specific foods, food allergy probably is the cause. Milk heads the list of allergenic foods. However, as indicated in the chart, all other foods must be suspected. Various allergists have reported the negative skin reactions to allergenic foods, especially when chronic or delayed symptoms are present. Because of the fallibility of the skin test, we have advocated certain standardized elimination diets¹⁶ for the study of possible food allergy. In chronic ulcerative colitis Mackie¹¹ has used such diets to determine allergenic foods, and we have used our modified fruit-free and cereal-free elimination diet as suggested in this article. As indicated in chart 1, skin testing has not been of any definite or uniform help in our diet trial. However, possible allergy has been suggested by disagreements with or distastes for specific foods, especially for milk, as obtained from the diet history (see Case 3).

When good results were obtained, relief was evident in from one to four weeks, and in the acute fulminating Case 5 it was definite in four days after the diet was initiated. In some cases maximum improvement required several months, probably because of the chronic tissue changes and the varying degree of secondary infection. Excellent results were obtained in six patients who failed to give a family or personal history of allergy. If allergy is a major cause in these patients, we must conclude that the colon is the only evident shock organ. The negative family history may be owing to lack of complete information.

In view of the benefit of the B vitamins, especially of thiamin and liver therapy as reported by Cheney,¹⁸ the possible effect of such treatment on these patients must be considered. In five of the most severe cases, no response to such treatment had been noted before the diet trial was begun. Of interest is the recent report of Shiffer and Ferguson¹⁷ that thiamin and liver injections were of no benefit in this disease. In Cases 1, 5, 7, 9 and 10 such therapy had not been used although good results were obtained with the elimination diet within three weeks. As previously stated, in all patients with chronic ulcerative colitis avitaminosis must be combated with proper therapy. Likewise anemia and hypoproteinemia must be treated specifically. This had been done along with diet trial when indicated in our patients. However, the good results, especially in those patients who

had received previous vitamin B and liver therapy, and in the patients in Cases 1 and 5 who received no additional vitamin therapy during the first month of dietary therapy, apparently were derived from the elimination diet.

Sulfonamide drugs were given by mouth while elimination diets were being used in Cases 3, 8 and 9. In Case 3 neoprontosil was administered for two weeks in two courses during the first six months after relief had occurred. The reduction from five or six to two to four soft stools indicated the possible alleviation of a mucosal infection. Proctoscopic examination showed that the scattered superficial ulcerations and a moderately purulent secretion also had decreased. This patient had received metaphen every few days by vein for two weeks before the diet was instituted. This medication was continued for three weeks thereafter. In view of this patient's complete recovery in the last three years and the results in our other cases, it is my opinion that relief did not depend on the metaphen. Sulfaguanidine was given in Case 8 for two weeks about two weeks after trial diet had been instituted. Failure to respond to previous sulfanilamide and sulfaguanidine therapy, however, and the definite relief in two weeks after diet trial was started indicate the probability that food allergy was the cause of the colitis. In Case 9 one or two formed stools per day occurred during the first two weeks of diet trial. However, the continuation of fever indicated that probably the infection in the bowel had persisted. For this reason sulfaguanidine was given for one and one-half months. Bergen's vaccine and a stock respiratory vaccine also were administered in the hope of increasing resistance to bowel organisms, although the fever disappeared in the first few days of such drug therapy and normal bowel movements had occurred before it was begun.

The failure of the sulfonamide drugs to produce definite benefits in Cases 3, 8 and 10 before diet trial was used and their failure in Cases 12, 13 and 15 in which septic temperatures were present and failure to respond to diet trial had occurred also indicate that in this disease they are not of the value anticipated.

SUMMARY

- 1 Allergic colitis, especially when caused by foods, results in diarrhea, mucus, bleeding, tenesmus, pain and cramping. This localized allergy produces inflammation, mucoid secretion, increased capillary permeability or smooth muscle spasm in varying degrees.

- 2 Chronic ulcerative colitis may be caused by severe allergic reactivity in the colonic mucosa similar to that responsible for atopic dermatitis. Ulcerations may arise from superimposed secondary infection from various bowel bacteria or possibly from lesions similar to canker sores in the mouth. Resultant ulcerations, mucosal denudation, fibrosis, scar tissue formation, and bowel perforation vary according to the degrees of resistance to infection.

- 3 Fruit-free elimination diets are recommended for the study of possible food allergy in these cases.

4 These diets are indicated especially in the acute fulminating and mild chronic cases. They may also be used in severe intractable cases as long as surgical treatment is not definitely indicated.

5 With such diets the maintenance of weight and the control of avitaminosis, hypoproteinemia, and anemia are necessary. The use of the sulfonamide drugs may benefit associated secondary infection.

6 That chronic ulcerative colitis may be due to inhalant or bacterial allergy must also be considered.

7 In intractable cases the study of possible allergy should not delay surgical treatment when it is obviously indicated.

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INTERCAPILLARY GLOMERULOSCLEROSIS *

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THIS syndrome of diabetes, hypertension and nephrosis was first described in 1936 by Kimmelstiel and Wilson³. They stressed the unusual and consistent pathological changes found in the kidneys, namely, degenerative changes in the walls of the capillaries, arterioles and vasa afferentia of the glomerular tufts. These authors reported eight cases with clinical and pathological findings. More recently Anson² reported six similar cases. Newburger and Peters,¹ in 1939, reviewed the two former papers and presented autopsy protocols of four cases and five cases in which the pathological renal lesions were suspected. A comprehensive analysis of the clinical, laboratory and pathological findings was included. Derow, Altschule and Schlesinger⁴ also published a detailed clinical and pathological report of one case. In the Cabot⁵ case reports of the Massachusetts General Hospital of July, 1940, appeared a rather unusual clinical and pathological report of a 22 year old girl who had had known diabetes for two and one-half years. This is the youngest case reported of this syndrome. Kimmelstiel and Wilson concluded that diabetes mellitus, hypertension, albuminuria, retinal vascular changes, a more or less well developed nephrotic syndrome, and impairment, in a varying degree, of renal function occurred in most of the cases in which the characteristic renal lesions were found. Most of the patients were elderly. Edema of a nephrotic type rather than that of renal or cardiac failure was a persistent finding. There was a constant marked albuminuria with or without nitrogen retention, indicating renal rather than cardiac involvement.

Newburger and Peters¹ listed the following clinical characteristics

- (1) All patients were over 40 years of age (except one that was 35) at the time of the onset of the diabetes or albuminuria or both
- (2) Fourteen of the 21 cases were women
- (3) Diabetes mellitus, usually mild in type, was present in all cases
- (4) Albuminuria, usually heavy, was present in a varying degree in all cases, especially before death occurred
- (5) Retinal arteriosclerosis was present in all cases, in addition papilledema, fresh hemorrhages, and exudates characteristic of the malignant phase of hypertension were present in five cases
- (6) Hypertension occurred in varying periods in all cases
- (7) Edema of some degree was present in the entire group, varying inversely to the level of the serum albumin, which in turn depended on the severity of the albuminuria and on the protein intake

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- (8) Heart failure when present was chiefly left sided
- (9) Low specific gravity of the urine, azotemia, and hypochromic anemia were commonly found

Two similar cases with autopsy reports are being presented which satisfy the criteria for this symptom complex. Both of these cases gave clinical evidence of extensive degenerative vascular changes.

CASE REPORTS

Case 1 A white woman, aged 59, was first seen in December 1937, at which time she was known to have had diabetes for four months, with suggestive symptoms for several years. The diabetes was under satisfactory control with insulin and diet. Her chief complaint was pain of a neuritic type in her extremities, which had been present in varying degree for two years.

The past history was irrelevant except for recurrent attacks of headache up to the menopause. She had been nauseated a great deal the past few years. In her young adulthood she had had a post-diphtheritic polyneuritis.

Physical examination revealed a rather poorly nourished white woman who appeared slightly older than her years, constantly complaining and obviously suffering from acute pain in her legs but able to walk. The relevant findings were a flushed, florid facies with a puffy appearance, bilateral clouding of the lenses of both eyes, marked arteriovenous nicking, and a silver wire appearance of the arteries of the fundi. The left border of the heart was 11 cm from the midsternal line in the sixth interspace. The blood pressure was 180 mm Hg systolic and 110 mm diastolic. The liver was palpated one finger's breadth below the right costal margin. The patellar and Achilles reflexes were not elicited even with reinforcement. However, the other reflexes were intact, and there were no sensory disturbances.

Laboratory reports at this time showed mild hypochromic anemia, normal blood serology, and a urine with a specific gravity of 1.012, albuminuria +++ (on a basis of 1-4), and a slight reduction of Benedict's solution. The blood sugar was 150 mg per 100 cc three hours after breakfast.

The neuritic pains gradually responded to large doses of vitamin B complex by mouth and massive doses of thiamin hydrochloride hypodermically. Anorexia with intermittent nausea and vomiting was persistent. Increasingly large amounts of insulin were required. At times she appeared slightly edematous especially about the face. Her systolic blood pressure gradually rose to over 200 mm of Hg with a diastolic pressure of over 110 mm. In July 1938, she was hospitalized because of intractable nausea and vomiting for which no definite cause was found. At this time the blood urea nitrogen was 22.9 mg per cent, nonprotein nitrogen 50 mg per cent, CO₂ combining power 55 vol per cent, blood sugar 155 mg per cent (fasting), and the bromsulphalein liver function test showed no dye retention. There was a persistent albuminuria and a low urinary specific gravity. Hemoglobin was 94 per cent. Spinal fluid was normal.

She was then quite well except for slight neuritic pains, general irritability, and occasional anorexia and nausea. She gained in insulin tolerance but her hypertensive level persisted.

In September 1939, her blood pressure was 240 mm Hg systolic and 120 mm diastolic, and she felt quite well aside from anorexia. She was started on potassium thiocyanate 1 gm daily. The vitamin B therapy was continued together with 0.045 gram of phenobarbital daily. Several weeks after this it was noticed that although she was eating very little her weight was gradually increasing. In October 1939, her blood pressure was 160 mm Hg systolic and 110 mm diastolic. During the first

week in November, the patient complained of a rapid gain in weight. There was edema of her ankles, she was slightly dyspneic, and her pulse rate was elevated so that digitalization was started. Weakness rapidly developed and nausea was present. Her temperature was 100.6° F, and pulse rate 94 per minute. She was generally edematous, especially in the face, with pitting edema of the extremities. She was again hospitalized on November 14, 1939, and became steadily worse. Edema persisted and later slight ascites developed. She had constant nausea and vomited nearly all ingested food. There was a low grade fever for several days after which it spiked to 102° F daily. She developed fluid in the right pleural cavity which was confirmed by fluoroscopy. A straw-colored sterile fluid was aspirated on two occasions.

She gradually developed a secondary anemia but her leukocyte count remained around 15,000 per cu mm with 30 to 40 per cent non-segmented polymorphonuclear cells. Heavy albuminuria was constantly present being as high as 3.5 per cent by volume with a specific gravity about 1.010. The blood urea nitrogen was 11 mg per 100 cc, the non-protein nitrogen 30 mg per 100 cc, the carbon dioxide combining power 67 volumes per cent, and the blood chlorides 313 and 370 mg per 100 cc on two occasions. Blood sugar determinations were constantly below 150 mg per 100 cc. With fluid formation in the right pleural cavity, dyspnea with the slightest exertion occurred. She developed a cough two days prior to her death, with some bloody sputum on several occasions.

The patient did not respond to treatment which consisted of intravenous infusions of sodium chloride and glucose solution, a blood transfusion, various diuretics, including mercurials, digitalization and other supportive measures. She died on December 2, 1939.

Pathological Report The usual ventral midline incision revealed rather edematous, pale abdominal fat.

There were approximately 75 cc of clear fluid in the right pleural cavity and 275 cc of turbid fluid in the left pleural cavity. The right lung was extremely congested throughout. The left lung was voluminous and deep red. There was a large hemorrhagic infarct in the upper lobe extending into the apex, having a base of 5 cm. A large hemorrhagic infarct involved almost the entire left lower lobe, and the pleural surface was covered with a fibrinopurulent exudate. The cut surfaces showed a diffuse pneumonitis in the remaining lung tissue.

The heart was enlarged, the walls hypertrophied and somewhat dilated. The right auricle showed a marked dilatation and contained a mural thrombus in the auricular appendage. The wall of the right ventricle was hypertrophied. There was a moderate amount of atheromatous deposits in the aorta which were progressive in degree distally. Approximately 4 cm above the junction of iliac arteries there was a small dissecting aneurysm of the posterior wall of the aorta, which extended only for a distance of approximately 3 cm. The entire vascular tree was sclerotic and presented numerous atheromatous plaques in the larger vessels.

The liver was enlarged and showed chronic passive congestion.

The pancreas showed interlobular fibrosis. The spleen was enlarged and markedly congested.

Both kidneys were enlarged and firm, and the capsules were moderately adherent. They showed a moderate amount of nephrosclerosis, and the pelvis showed some increase in fat. The ureters and bladder showed no definite abnormalities. Microscopic report (see under Case 2).

*Case 2** A white male was referred to Dr. Hobart Rogers for treatment of diabetes mellitus in April 1937, a condition the patient had been aware of for six months. He had always been obese, his average weight being 240 pounds, up until five years previously when he gradually began to lose weight, the reduction being

* We are indebted to Dr. Hobart Rogers for the data on this case.

more rapid the past year. During the past three years he had had periods of polydipsia and polyuria lasting for a month or so. However, these symptoms were never marked. There had been generalized pruritus during the past six months.

He complained of pain and stiffness in the right shoulder. He also suffered from angina of effort.

His past history was irrelevant. The family history revealed no pertinent information except that there was one brother with diabetes mellitus.

Physical examination on April 5, 1937, revealed an obese white male weighing 187 pounds, 66 $\frac{3}{4}$ inches in height, with a temperature of 97.4° F, pulse of 70 per minute, and a blood pressure of 180 mm Hg systolic and 85 mm diastolic. The mouth was edentulous, the lungs were clear, and the left border of the heart was one inch outside the midclavicular line in the fifth left interspace. There was a blowing systolic murmur of moderate intensity heard over the apex and over the precordium and somewhat higher pitched at the aortic area. The reflexes were generally diminished. The dorsalis pedis pulsations were barely perceptible.

Laboratory data at this time showed a negative Kline test, heavy glycosuria (other date was not recorded), blood sugar of 299 mg per 100 cc.

Fluoroscopy of the chest showed enlargement of the left ventricle of the heart and arteriosclerotic changes in the aorta. The electrocardiogram showed maximum normal A-V conduction-line, left axis deviation and low amplitude of the T-waves.

The patient was placed on a diabetic régime with a low caloric diet and insulin. He rapidly gained in insulin tolerance so that by July his dosage had been reduced from 66 to 30 units daily. The anginal pain was more frequent when the blood sugar was reduced to a normal level. The shoulder discomfort responded to symptomatic treatment. By August 1938, the insulin requirement had dropped to 8 to 12 units of protamine zinc insulin daily. Later the patient had less anginal pain with a reduction of his diet without insulin. His weight was 208 pounds. He complained at various times of nausea and pain across his lower abdomen. In March of 1939 the patient developed dyspnea on exertion, ankle edema and ascites. He was digitalized and given mercurial diuretics with good relief. At this time his weight was about 190 pounds.

In November 1939, the patient had a typical attack of coronary occlusion which was verified by an electrocardiogram which also suggested increased myocardial damage. The patient had edema and spells of weakness and breathlessness. He responded fairly well following this episode, but after January 1940, the edema of the legs and sacrum was more marked, and there was heavy albuminuria with hyaline casts in the urine.

At this time the blood urea was 21 mg per 100 cc and blood sugar 190 mg per cent. The blood pressure was 160 mm Hg systolic and 100 mm diastolic. He became confused and irritable, amblyopia developed, and there was increased peripheral edema. Liver enlargement became noticeable but mercurial diuretics controlled the edema fairly well. At this time a diagnosis of intercapillary glomerulosclerosis was made. In March 1940, there was a severe gastrointestinal hemorrhage, thought to be due to esophageal varices, secondary to cirrhosis of the liver. After this the patient declined rapidly and died suddenly on March 9, 1940.

Pathological Report The abdominal cavity contained about a liter of lightly bile stained fluid. On the lesser curvature of the stomach about two inches proximal to the pylorus there was a chronic ulcer 2 cm in diameter with a smooth base and indurated edges. Sclerotic vessels could be seen on the peritoneal side of the ulcer base.

The liver was large and firm with a sharp edge which was cut with increased resistance. The gall-bladder contained a solitary stone 2 cm in diameter.

The kidneys were about normal in size and the right showed two small scars. The capsules stripped fairly easily. Section of the kidneys experienced increased resistance. The cortex was thin and fibrotic.

The pleural cavities were dry and the lungs crepitant throughout. Subpericardial fibrosis was present about the pericardium. There was evidence of two old myocardial infarcts near the apex. The surfaces made by cutting revealed these areas to be thin and soft. Subendocardial fibrosis was also evident. The orifices of the coronary arteries were slightly constricted and the coronary arteries showed atherosclerosis throughout their courses.

Microscopic Report The microscopic sections taken from the kidneys of both cases showed various stages of sclerosis of the glomeruli, ranging from early fibroblastic proliferation to hyalinization. The earlier and intermediary stages showed a relatively well preserved capillary system within the glomeruli with fibrosis between the tufts (intercapillary fibrosis). Differential stains showed the capillaries in these stages to be intact with fibrous proliferation in the intercapillary spaces.

DISCUSSION

As Newburger and Peters have stated, the pathogenesis of this disease seems to depend upon the severe and extensive arterial and arteriolar degeneration associated with diabetes mellitus, hypertension, and renal damage. The two cases presented gave evidence of far advanced vascular degeneration with retinal artery sclerosis, hypertension and persistent albuminuria.

Only with the earlier recognition of this syndrome may it be possible to obtain more information concerning the contributing and causative factors and make more successful methods of therapy available. Even then there is no assurance that the progression of the pathological processes can be retarded. Both of the cases presented were recognized in the terminal stages. Studying the pathogenesis in retrospect, it is hard to determine what other procedures, methods or drugs might have been more efficacious.

SUMMARY

Two additional cases of intercapillary glomerulosclerosis have been presented.

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TRANSITORY PULMONARY INFILTRATIONS MISTAKEN FOR TUBERCULOSIS, WITH A REPORT OF FIVE CASES^{*}

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For some time the chest roentgenogram has been the most valuable diagnostic measure in the recognition of pulmonary tuberculosis. It has been shown repeatedly that physical examination of the chest as the only procedure in the diagnosis of pulmonary diseases is entirely inadequate. Spellman¹ gives an illuminating exposition of this fact in a recent article relating the experience of attempting, by physical examination, to detect pulmonary tuberculosis in army recruits in 1917-1918. It is not the purpose of the present authors, therefore, to minimize the efficacy of the roentgenogram in the diagnosis of pulmonary tuberculosis.

Five patients are presented, whose chest roentgenograms showed densities strikingly simulating tuberculous infiltrations which, however, proved to be non-tuberculous. In each of the five cases a diagnosis of pulmonary tuberculosis was originally made by one or more competent roentgenologists or phthisiologists. From the data available at the time the five patients were first observed the diagnoses were not questioned by the present writers. However, doubt was cast on the original diagnoses when examination of the sputum and aspirated gastric contents with direct smears, concentrations, cultures or guinea pig inoculations failed to disclose the presence of tubercle bacilli. Subsequent serial roentgenograms confirmed the non-tuberculous etiology of the pulmonary infiltrations.

To venture a diagnosis on a single roentgenogram of a patient's chest frequently leads to error. The demonstration of tubercle bacilli in the sputum should be the criterion in the final diagnosis of broncho-pulmonary tuberculosis. Probably in almost 100 per cent of the cases of active pulmonary tuberculosis tubercle bacilli can be found, if sufficiently thorough searches are made. If tubercle bacilli are absent, it is a safe rule to consider the pulmonary pathologic changes non-tuberculous in nature and to proceed with the various special examinations, such as bronchoscopy, etc., in order to arrive at a diagnosis.

With the universal use of artificial pneumothorax therapy in pulmonary tuberculosis the above remarks are pertinent. The value of this form of therapy in pulmonary tuberculosis is established beyond any doubt, but it may be unnecessary or even harmful in other pulmonary diseases. In the zeal for rehabilitating the tuberculous individual patient it is wise to establish first whether the patient has tuberculosis.

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From the Workmen's Circle Sanatorium, Liberty, New York

CASE REPORTS

Case 1 S S, male, aged 51 years, was admitted to the Workmen's Circle Sanatorium on May 24, 1939. For the past 15 years he had been the owner of a confectionery store. Prior to that time he had worked as a tailor. He did not recall any childhood illnesses. He had had pneumonia 18 years previously and a tonsillectomy 15 years previously. At intervals, for many years, the patient had had attacks of moderate dyspnea which he attributed to asthma. These episodes did not inconveni-

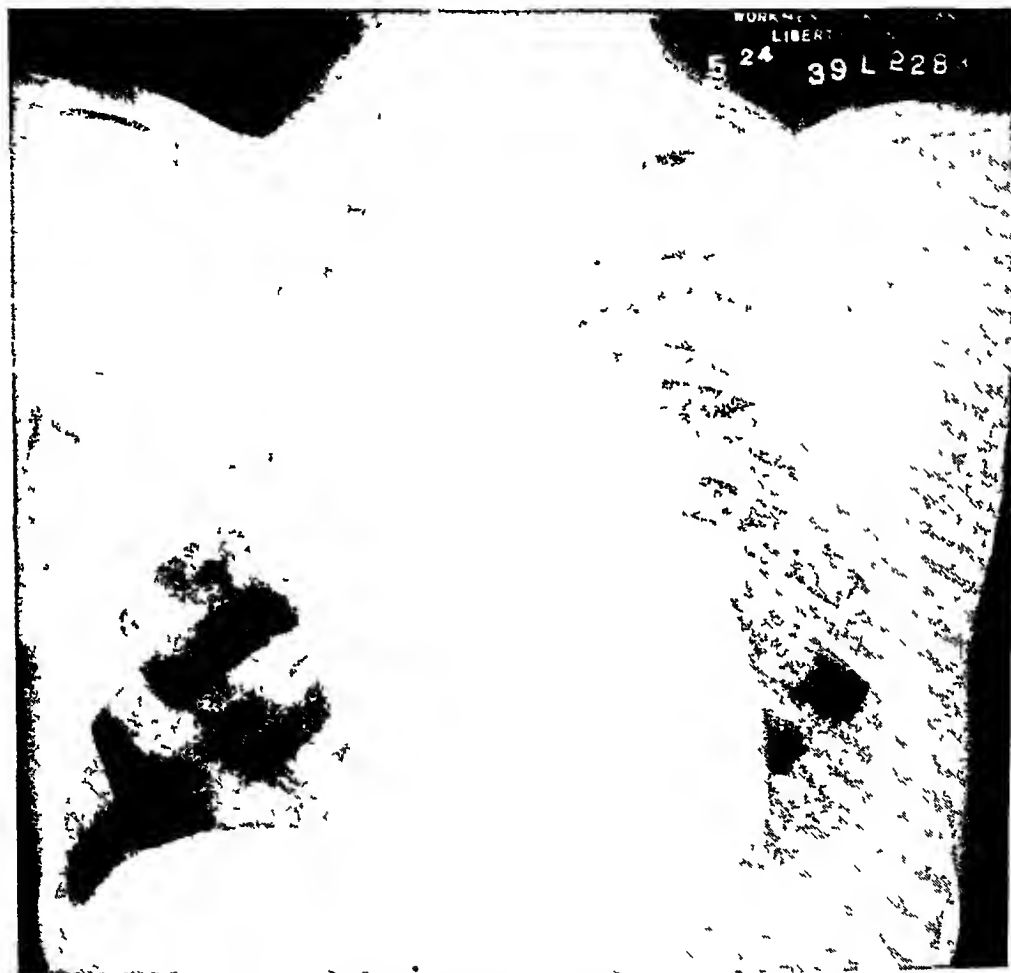


FIG 1 (Case 1) Roentgenogram taken May 24, 1939. Dense infiltrations throughout the left lung and the upper two thirds of the right lung. The cardiac silhouette is moderately enlarged particularly to the left.

ence him very much and he did nothing about them. The patient's story of the onset and symptoms of his present illness was also rather vague and indefinite. About six weeks prior to his admission to the Sanatorium he began to feel weak, lose appetite and weight, and he began to have pain over the left side of his chest. He visited a physician who referred him for a roentgenogram of his chest. A diagnosis of pulmonary tuberculosis was made, and he was advised to enter a sanatorium.

The noteworthy findings on the patient's admission to the sanatorium were poor nutrition, pale, dry skin, pale nasal mucosa, enlarged right tonsil and slight congestion of vocal cords. On physical examination the heart did not show any enlargement.

rate was 108 per minute, rhythm was regular, sounds were of good quality, no murmurs were heard, the second pulmonic sound was accentuated. Blood pressure was 90 mm Hg systolic and 62 mm diastolic. Physical examination of the lungs showed dullness, bronchovesicular breathing, and medium moist râles over the right upper lobe anteriorly and posteriorly. Sibilant and sonorous râles were heard over the entire left lung anteriorly and posteriorly with bronchovesicular breathing over the

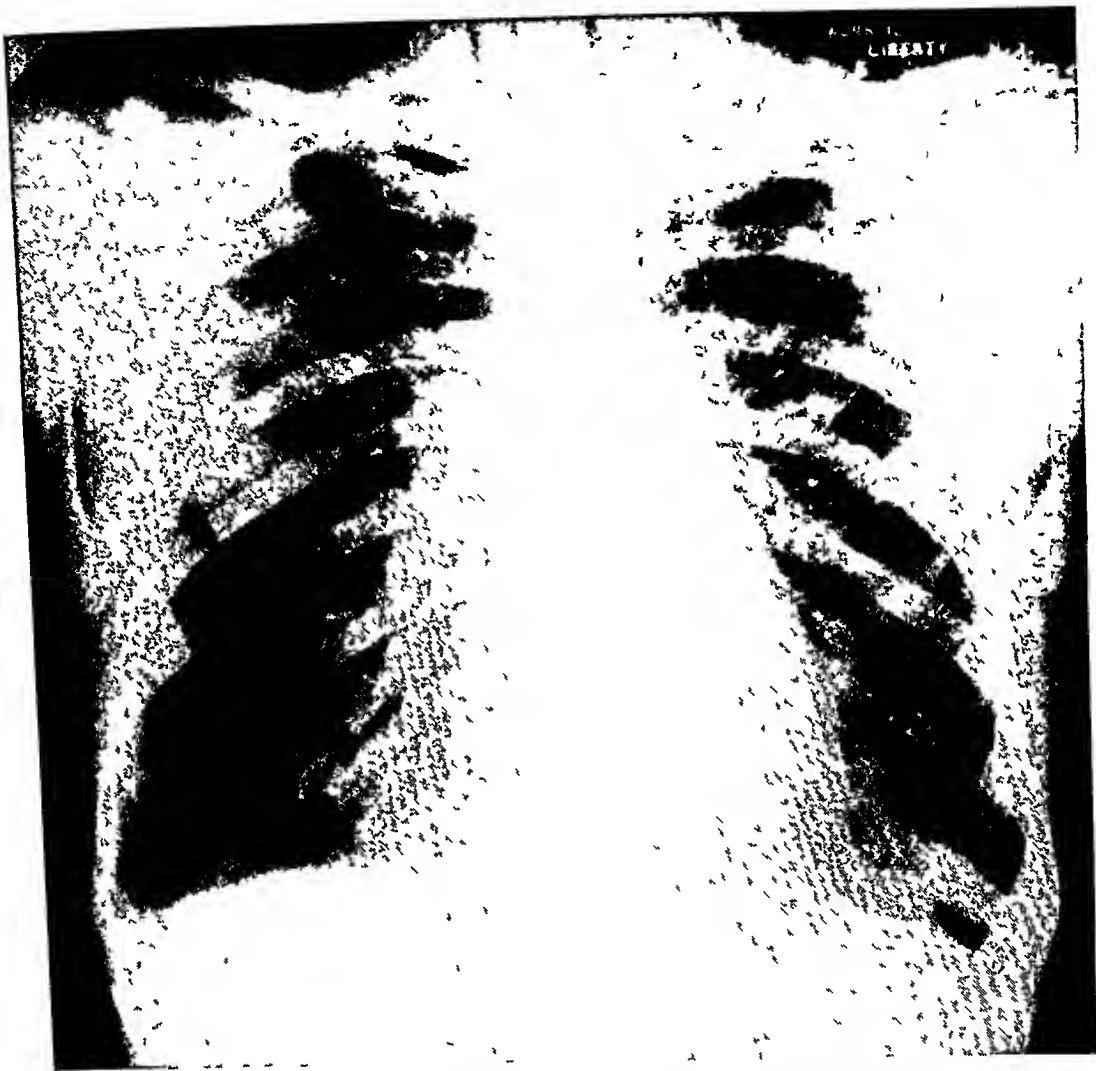


FIG 2 (Case 1) Roentgenogram taken July 5, 1939. Complete clearing of the right lung field, slight infiltration left upper lobe. The cardiac silhouette remains enlarged with straightening of the left border.

upper lobe and dullness over the base. There was cyanosis of the finger nails and feet. Both legs showed marked varicosities.

Laboratory Data May 25, 1939. Urinalysis was negative. The blood count showed hemoglobin, 86 per cent, red blood cells, 4,460,000 per cu mm, white blood cells, 19,300 with polymorphonuclears, 43 per cent, lymphocytes, 48 per cent and eosinophiles, 9 per cent. Erythrocyte sedimentation rate, 54 mm in one hour, Kahn reaction negative, non-protein nitrogen, 28.5 mg in 100 cc of blood. On August 14, 1939, the hemoglobin was 92 per cent, red blood cells, 4,740,000, white blood cells, 17,450 with polymorphonuclears, 74 per cent, lymphocytes, 20 per cent, monocytes 1 per cent and eosinophiles, 5 per cent. The erythrocyte sedimentation rate was 5 mm.

in one hour. Seven sputum examinations, including four of concentrated sputum, and culture did not show the presence of tubercle bacilli. Vital capacity (May 25, 1939) 1500 cc. An electrocardiogram taken on May 24, 1939, showed an auricular and ventricular rate of 110 and right axis deviation, otherwise within normal limits. The electrocardiogram was repeated on June 19, 1939, following the administration of



FIG 3 (Case 1) Roentgenogram taken September 5, 1939. Both lung fields clear. Cardiac silhouette normal in size and configuration.

digitalis, and it showed a depression of the R-T segments in Leads II and III, otherwise it showed no change from the previous electrocardiogram. Another electrocardiogram taken on August 17, 1939, showed an auricular and ventricular rate of 90, and it was otherwise unchanged from the first electrocardiogram, taken on May 25, 1939.

Roentgenograms On May 24, 1939, a chest roentgenogram (figure 1) of this patient showed dense infiltrations throughout the left lung and upper two-thirds of the right lung. The cardiac silhouette showed moderate enlargement particularly to the

left Fluoroscopic examination of the heart revealed slight enlargement of the left ventricle and more marked enlargement of the right ventricle. On June 13, 1939, the roentgenogram showed marked clearing of both lung fields, there was no change in size or configuration of the cardiac silhouette. On July 5, 1939, the roentgenogram (figure 2) showed complete clearing of the right lung field and remaining slight infiltration in the left upper lobe. The cardiac silhouette remained enlarged with straightening of the left border. On August 5, 1939, the chest roentgenogram was within normal limits except for evidence of emphysema. The straightening of the left border of the cardiac silhouette was not as marked as in the previous film. The last roentgenogram (figure 3), on September 5, 1939, showed no change in the lung fields from the film taken on August 5, 1939. The cardiac silhouette had returned to normal in size and configuration.

Course On admission to the Sanatorium the patient was moderately dyspneic. There was also cyanosis of the finger nails and feet. That of the latter might have been due, in part, to the varicosities of both legs. Digitalis was administered, but was discontinued owing to its apparent lack of effect on the heart rate and the dyspnea. After about six weeks' stay in the Sanatorium the dyspnea and cyanosis began to subside, and prior to discharge the patient had no greater amount of dyspnea than would be expected in any individual with moderate emphysema. The cyanosis had completely disappeared. The patient ran an afebrile course and gained 13 pounds in weight. During his entire stay in the sanatorium the amount of cough and expectoration was negligible. The patient was discharged on September 17, 1939, and he returned to his usual activities.

Comment In this case the original diagnosis of pulmonary tuberculosis was based essentially on the roentgen findings. Subsequent observation proved that the diagnosis was incorrect. In attempting to arrive at a correct diagnosis left-sided heart failure with one or a combination of the following common complications was considered, namely, pulmonary engorgement, pulmonary edema, pulmonary infarction and bronchopneumonia. However, the visualization, on fluoroscopic examination, of relatively more pronounced enlargement of the right ventricle, the accentuation of the second pulmonic sound, and the evidence of right axis deviation on the electrocardiogram, all pointed essentially to a right ventricular strain. Evidence was also lacking of the presence of hypertension, coronary arteriosclerosis, and mitral or aortic valvular disease, which tended to confirm the impression that the clinical picture was one of cor pulmonale. Apparently, the pulmonary manifestations were not the result of left ventricular insufficiency but rather due to the fact that the pathologic changes in the lungs produced increased resistance in the pulmonary circuit, with consequent hypertension in the pulmonary artery, followed by dilatation and possible hypertrophy of the right ventricle. The nature of the pulmonary infiltrations will be discussed later.

Case 2 F K, female, aged 26 years, a school teacher, was admitted to the Workmen's Circle Sanatorium on November 2, 1937, during the fourth month of her first pregnancy. In childhood she had whooping cough, measles, chicken pox and influenza. Two weeks prior to admission she was taken acutely ill with fever and cough productive of about two drams of yellowish sputum in 24 hours. She was seen by two phthisiologists who diagnosed pulmonary tuberculosis and advised immediate admission to a sanatorium and induction of artificial pneumothorax. Interruption of the pregnancy was considered but not carried out.

The noteworthy physical findings on the patient's admission to the sanatorium were mild anemia of finger nails and eyelids, obvious symmetrical enlargement of thyroid, palpable but not markedly enlarged submaxillary glands, slight malar flush, and moist skin. The pharynx was slightly congested, and the anterior pillars and epiglottis were injected. The heart was entirely negative. Blood pressure was 94 mm Hg systolic and 68 mm diastolic. The abdomen was slightly protuberant, the uterus was enlarged midway between the symphysis and umbilicus. The lungs showed

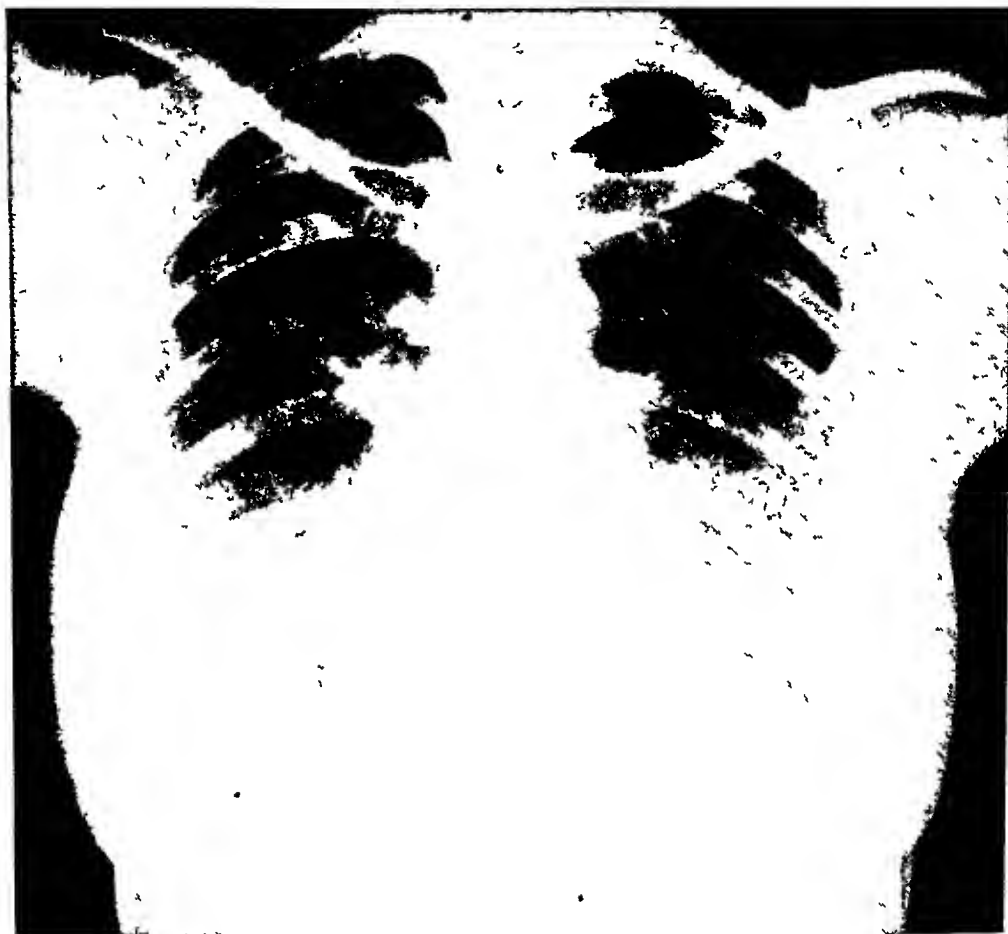


FIG 4 (Case 2) Roentgenogram taken October 28, 1937. Infiltration in the right infraclavicular region with bronchogenic spread to the right base.

bronchovesicular breathing over the right upper lobe anteriorly, dullness over the right upper lobe posteriorly, distant bronchial breathing, and medium moist râles from the right angle of the scapula to the base.

Laboratory Data November 3, 1937. Urinalysis negative. The blood count showed hemoglobin, 70 per cent, red blood cells, 4,000,000 per cu mm, white blood cells, 10,200 with polymorphonuclears, 73 per cent, lymphocytes, 22 per cent and monocytes, 5 per cent. Erythrocyte sedimentation rate, 59 mm in 60 minutes. Kahn test was negative. On November 21, 1937, the blood count was as follows: hemoglobin, 68 per cent, red blood cells, 3,950,000, white blood cells, 8,000 with polymorphonuclears, 65 per cent, lymphocytes, 30 per cent, monocytes 2 per cent and

eosinophiles, 3 per cent Erythrocyte sedimentation rate, 36 mm in 60 minutes Five sputum examinations, including three of concentrated sputum, and one culture did not show the presence of tubercle bacilli

Roentgenograms A chest roentgenogram (figure 4), taken on October 28, 1937 (prior to admission), showed infiltration in the right infraclavicular region with bronchogenic spread to the base The left lung was negative The roentgenogram taken on November 3, 1937, on admission to the sanatorium, showed no change from

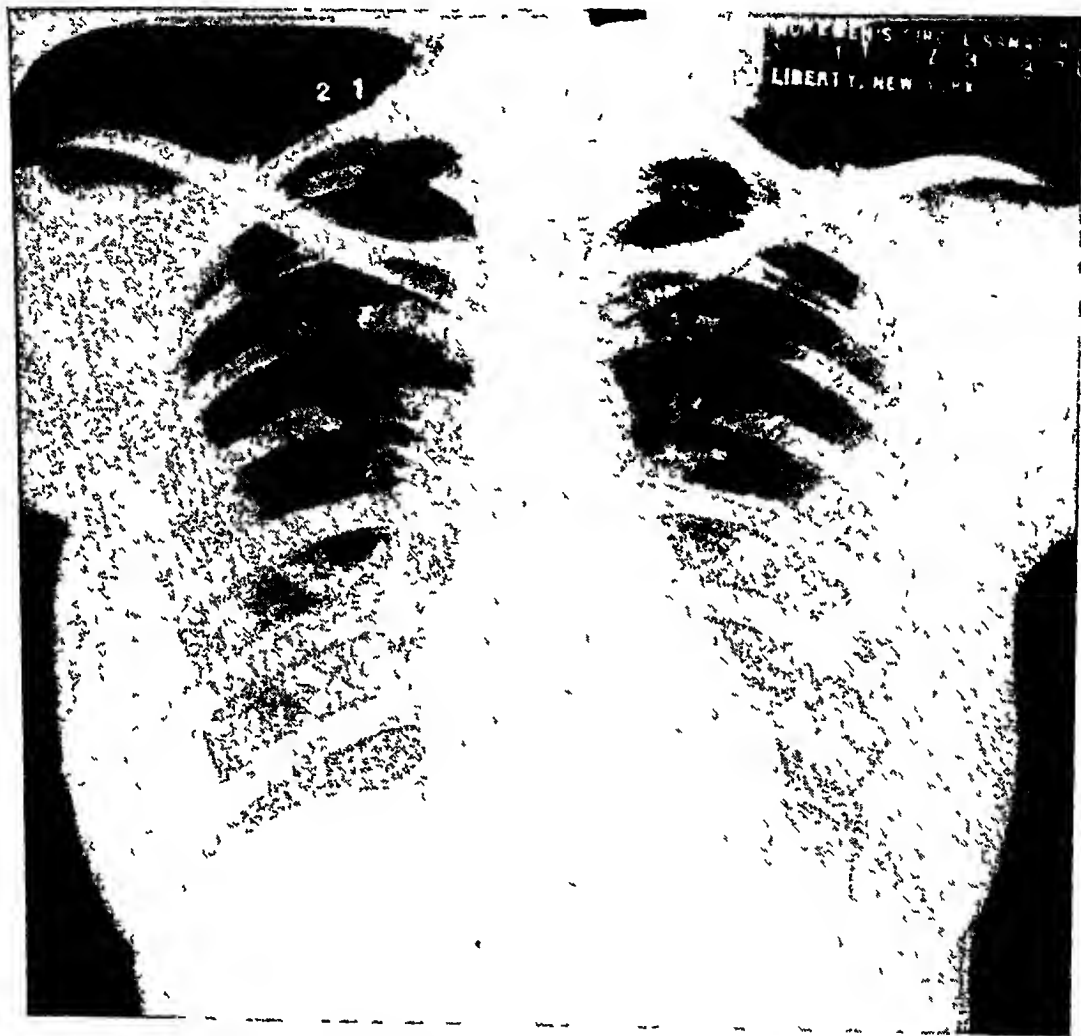


FIG 5 (Case 2) Roentgenogram taken November 13, 1937 Marked clearing of the right lung field

the previous film On November 13, 1937, a roentgenogram (figure 5) showed marked clearing of the right lung field so that only accentuation of the lung markings remained The left lung was negative A roentgenogram taken on November 20, 1937, showed no evidence of any abnormal changes in either lung

Course During the patient's stay in the sanatorium she ran an afebrile course and gained two pounds in weight The productive cough subsided, and prior to discharge, disappeared entirely She was discharged from the sanatorium on November 21, 1937 At term she had an uneventful delivery To date she has shown no evidence of having any active pulmonary tuberculosis

Comment This is another illustration of a mistaken diagnosis of tuberculosis based on the roentgenogram. The original diagnosis was disproved by serial roentgenograms, which showed the rapidity with which resolution of the pulmonary infiltration took place, and the failure to find tubercle bacilli in the sputum. This patient had a non-tuberculous bronchopneumonia resembling in many respects the type described by Reimann and Havens². The causative agent is thought to be a filtrable virus. Unfortunately, typing of the sputum was omitted at the onset of the illness prior to admission to the sanatorium.

Case 3 E. P. male, aged 23 years, clerical worker, was seen by one of the present writers (A. A. K.) on July 23, 1933. In childhood he had had measles. On July 22, 1933 the patient developed what he termed a "cold" accompanied by an unproductive cough. He felt somewhat feverish but did not take his temperature, and he did not feel sufficiently ill to go to bed. When the patient appeared for examination the

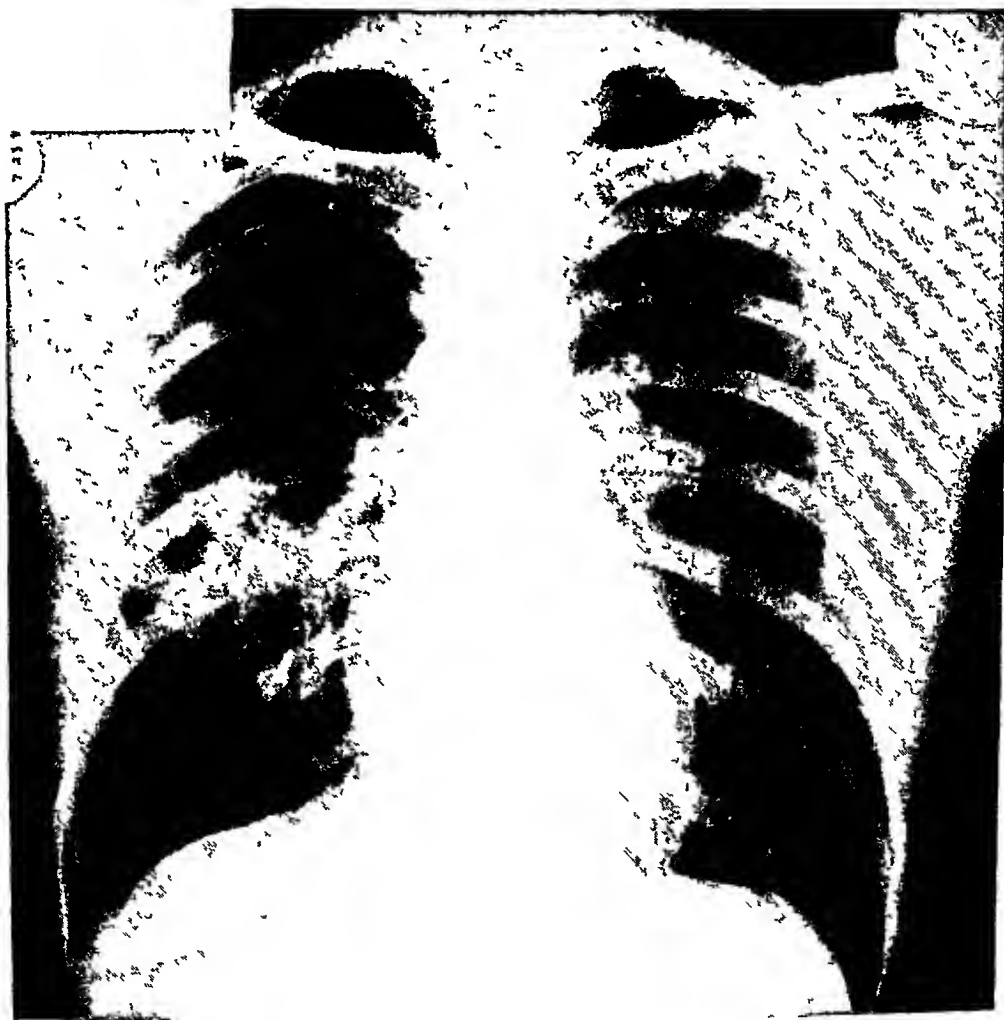


FIG 6 (Case 3) Roentgenogram taken July 23, 1933. Infiltration in the right lung between the fourth and fifth anterior ribs.

following day he had a temperature of 102.4° F. His only other complaint was that of cough, which had become somewhat productive of yellowish sputum.

The significant findings on examination were congestion of the pharynx and epiglottis. The lungs and heart were entirely negative, and the blood pressure was 120 mm Hg systolic and 80 mm diastolic. There were no other noteworthy physical findings.

Laboratory Data July 24, 1933. Urinalysis negative. The blood count showed hemoglobin, 90 per cent, red blood cells, 4,600,000 per cu mm, white blood cells, 8,700 with polymorphonuclears, 76 per cent, lymphocytes, 22 per cent, monocytes, 1 per cent and eosinophiles, 1 per cent. Erythrocyte sedimentation rate, 36 mm in 60 minutes. Wassermann reaction was negative. Eight sputum examinations and inoculation of guinea pigs with two sputum specimens, collected on different days, did not show the presence of tubercle bacilli.

Roentgenograms A chest roentgenogram (figure 6), taken on July 23, 1933, showed infiltration in the right lung between the fourth and fifth ribs anteriorly. The remainder of the right lung and the left lung showed accentuation of the lung markings. On July 27, 1933, the chest roentgenogram showed almost complete clearing of the infiltration in the right lung field. The accentuation of the lung markings in both lungs was still present. On August 3, 1933, the roentgenogram showed complete clearing of the infiltration in the right lung field. Some accentuation of the lung markings in both lungs was still evident. On August 10, 1933, the roentgenogram (figure 7) showed no abnormal changes.

Course Four days after the onset of symptoms the patient's temperature returned to normal. The productive cough disappeared in a week. He was kept in bed about three weeks. After three months, when it was definitely determined that the inoculated guinea pigs did not show any evidence of tuberculous infection, the patient was allowed to return to his usual activities of life. This patient has been observed from 1933 until the present time, chest roentgenograms have been taken at least once yearly. To date there has been no evidence of any active pulmonary tuberculosis.

Comment Following the first roentgenogram this patient's case was reviewed by a group of phthisiologists at a tuberculosis sanatorium conference. The diagnosis of pulmonary tuberculosis was not questioned and induction of an immediate pneumothorax was recommended. As in the previous case, the diagnosis was non-tuberculous bronchopneumonia probably caused by a filtrable virus. Since the episode occurred during the month of July it seemed rather remote, during the first few days of the patient's illness, to identify the clinical picture with that of epidemic influenza bronchopneumonia. The serial roentgenograms pointed to the non-tuberculous nature of the pulmonary infiltrations. The absence of tubercle bacilli confirmed that impression. It would have been of interest to have had this patient's sputum typed. Unfortunately it was not done.

Case 4 I. R., male, aged 48, a dress manufacturer, was admitted to the Workmen's Circle Sanatorium on July 15, 1940. In childhood he had had an appendectomy and in 1918 he had had the "flu." He did not recall any other specific illnesses in the past. For a number of years the patient had had a productive morning cough which he attributed to smoking. In May 1940 his cough became more marked. At about the same time he lost his appetite and began to lose weight and strength. He also began to have night sweats. The patient consulted a physician, a chest roentgeno-

gram was taken, and a diagnosis of tuberculosis was made. Immediate admission to a sanatorium and induction of artificial pneumothorax were advised.

The significant physical findings on admission to the sanatorium were moderate congestion of the pharynx, deviation of the nasal septum to the right with beginning atrophy of the mucosa, markedly retracted and thickened right ear drum, and slightly retracted left ear drum. The lungs and heart were entirely negative. Blood pres-

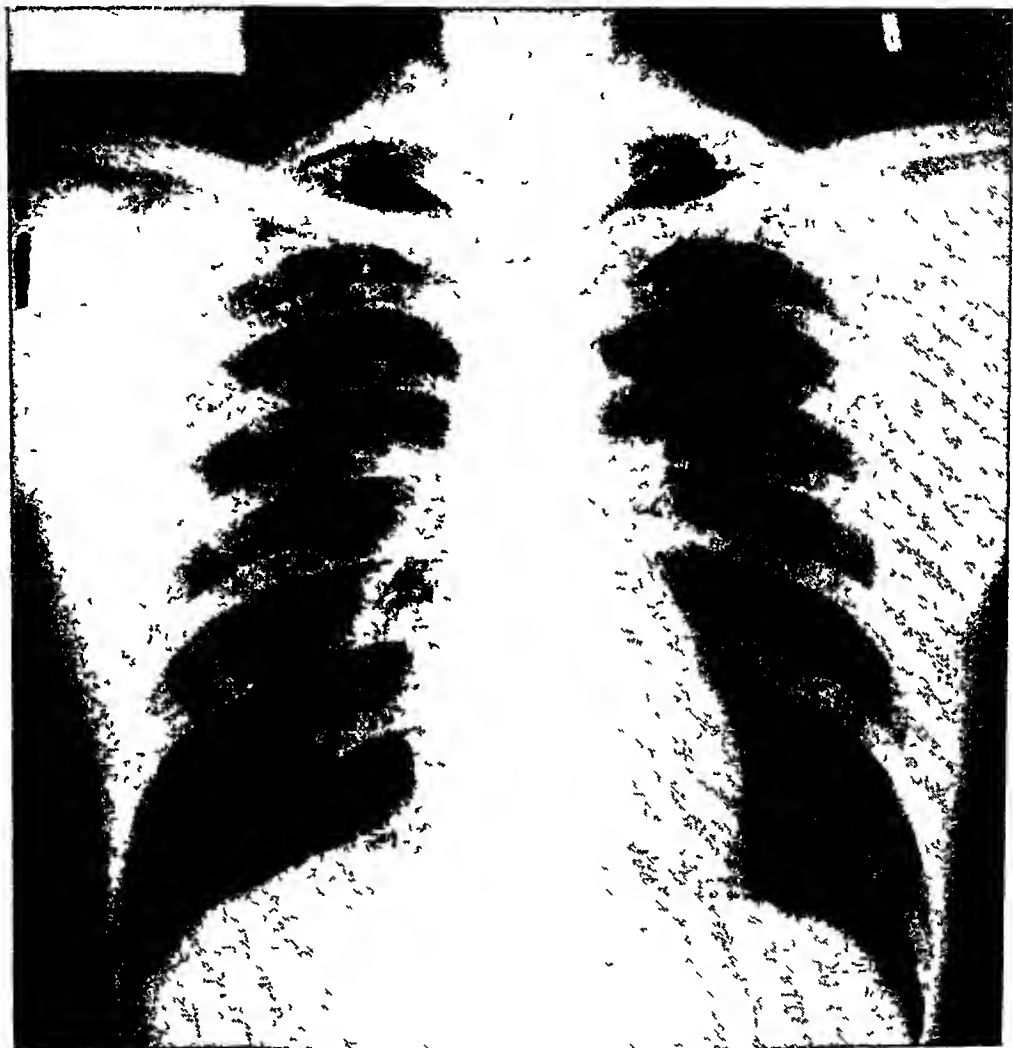


FIG 7 (Case 3) Roentgenogram taken August 10, 1933. Complete clearing of the infiltration in the right lung.

sure was 106 mm Hg systolic and 70 mm diastolic. Except for a linear scar over the abdomen, at McBurney's point, the remainder of the physical examination showed nothing noteworthy.

Laboratory Data July 17, 1940. Urinalysis negative. The blood count showed hemoglobin, 90 per cent, red blood cells, 4,560,000 per cu mm, white blood cells, 10,700 with polymorphonuclears, 43 per cent, lymphocytes, 55 per cent, monocytes, 1 per cent and eosinophiles, 1 per cent. Erythrocyte sedimentation rate, 12 mm in 60 minutes. Kahn test was negative. Non-protein nitrogen 30 mg in 100 cc of blood.

Six sputum examinations, including three of concentrated sputum, and one culture did not reveal the presence of tubercle bacilli. The vital capacity was 3200 c.c. An electrocardiogram showed low voltage of the Q R S complexes in all three leads, an isoelectric T₁, and left axis deviation.

Roentgenograms A chest roentgenogram (figure 8), taken on July 2, 1940 (prior to admission), showed infiltration in the right upper lobe with an area of

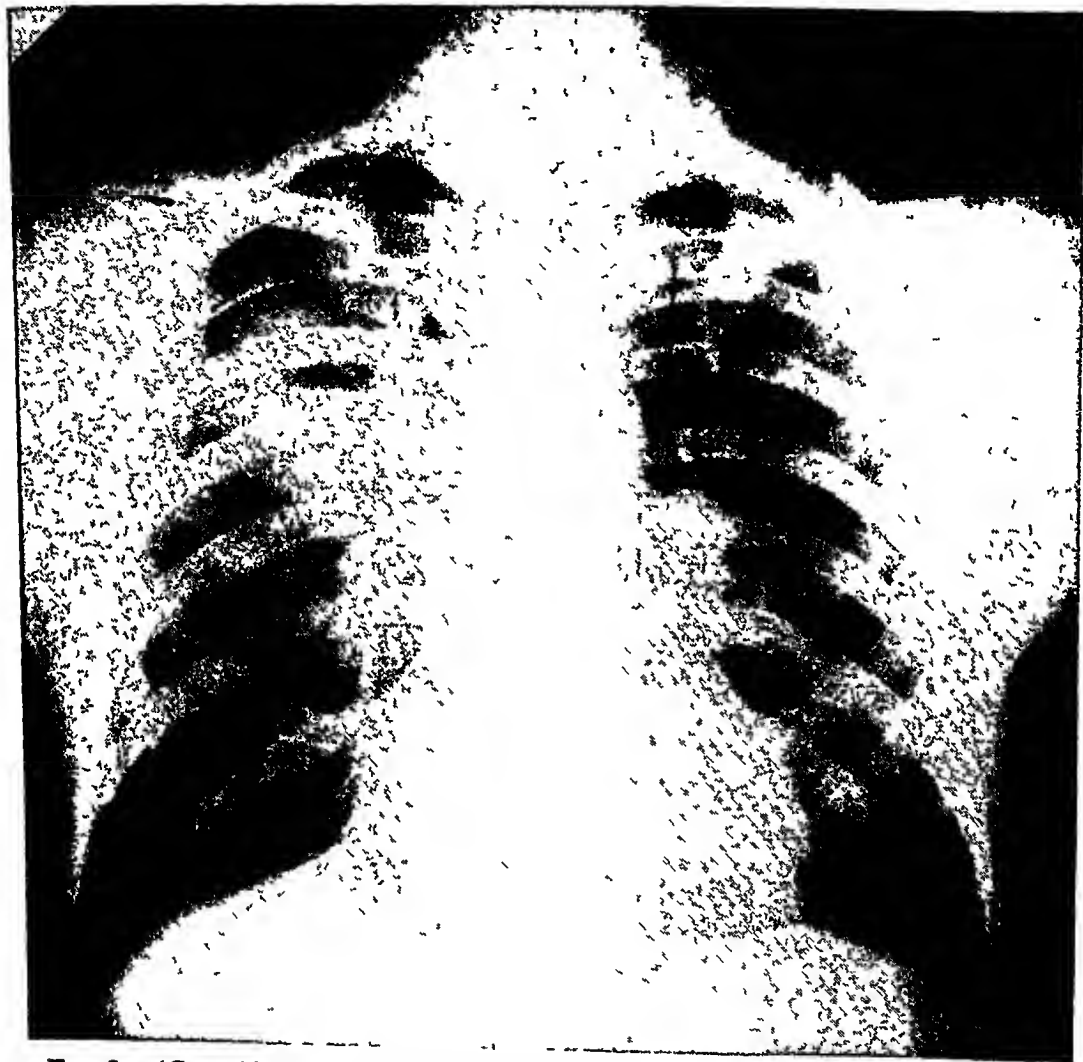


FIG 8 (Case 4) Roentgenogram taken July 2, 1940. Infiltration in the right upper lobe with an area of rarefaction suggestive of cavitation at the level of the second anterior rib.

rarefaction suggestive of cavitation at the level of the second rib anteriorly. The left lung was negative. The roentgenogram taken on admission to the sanatorium, on July 13, 1940, showed infiltration in the right second interspace external to the hilus region. There was no evidence of rarefaction, and the left lung was negative. A roentgenogram (figure 9), taken on August 20, 1940, showed almost complete clearing of the infiltration in the right lung, leaving a few fibrotic strands external to the hilus region. A roentgenogram taken on September 12, 1940, showed no change from the one taken on August 20, 1940.

Course. During the patient's stay in the sanatorium he ran an afebrile course and gained 18 pounds in weight. Except for a morning cough, productive of about

15 c c of mucopurulent sputum, he was symptomless. An attempt was made to obtain a bronchogram following lipiodol instillation. The bronchogram did not show any evidence of bronchiectasis. However, the bronchogram could not be considered conclusive because lack of cooperation on the part of the patient resulted in poor filling of the bronchial tree. Bronchoscopic examination was recommended but the patient refused to have that procedure performed because he claimed that he felt well and required no further treatment. He left the sanatorium against medical advice on September 13, 1940.

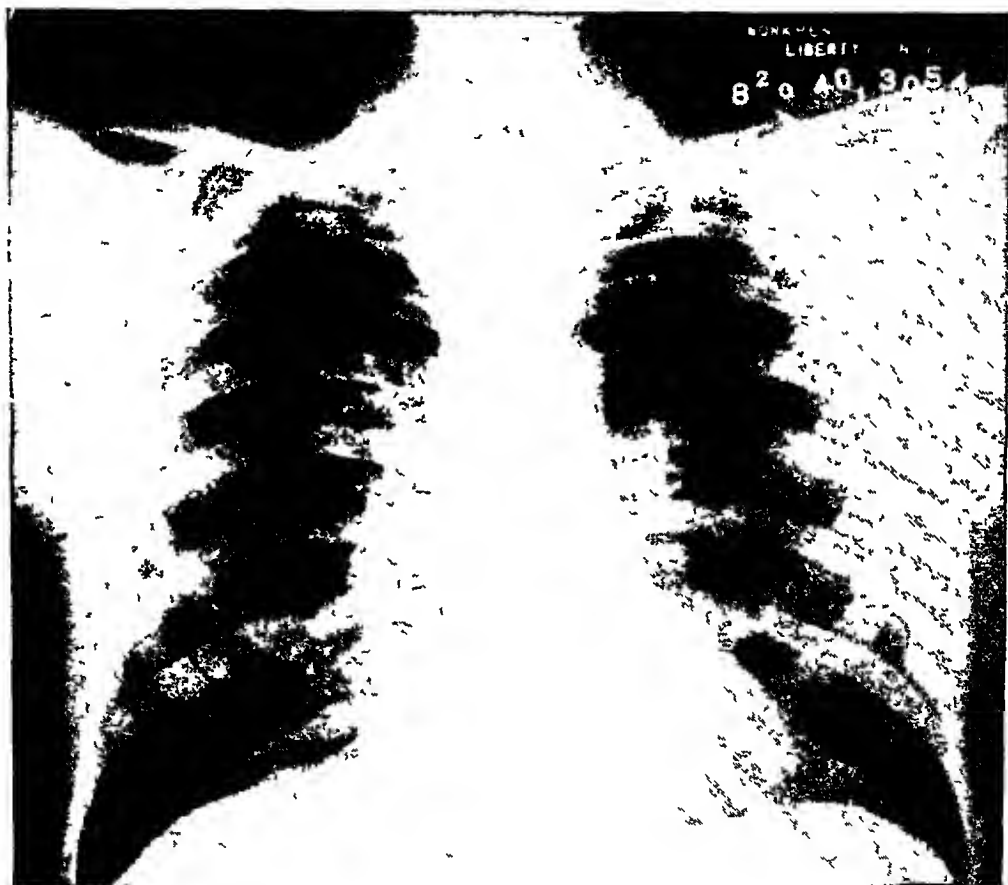


FIG 9 (Case 4) Roentgenogram taken August 20, 1940. Almost complete clearing of the infiltration in the right lung, no evidence of rarefaction.

Comment It is obvious that the infiltration in this patient's right lung was not tuberculous in origin. Although conclusive evidence is lacking, it is felt that this patient had had a bronchial infection for some time and that the density in the right upper lobe, seen on the first roentgenogram (figure 8), was due to lobular atelectasis resulting from temporary plugging of a bronchus. It is difficult to account for the suggestive cavity in the right upper lobe. It is possible that there was beginning necrosis in the lobular atelectatic area, the patient emptying the necrotic material spontaneously when plugging of the bronchus was no longer present.

Case 5 S M. F, male, aged 39 years, a salesman, was seen by one of the present writers (E S) on July 18, 1939. On May 30, 1939, the patient was taken ill with a productive cough, slight elevation of temperature, and occasional mild wheezing, but no frank asthmatic attack. He consulted a physician who referred the patient to a roentgenologist. A roentgenogram of the chest was taken and a diagnosis of resolving pneumonia or tuberculosis in the right lung was made. The subjective symptoms



FIG 10 (Case 5) Roentgenogram taken May 31, 1939. Dense infiltration involving almost the entire right lung. Increase in lung markings throughout the left lung.

subsided in a few days. About one week after the onset of the present illness the patient had an attack of dyspnea which was diagnosed as bronchial asthma by his physician who administered adrenalin and ephedrine, giving the patient some relief. Immediately following this episode the patient began to cough again. He perspired freely, there was slight elevation of temperature, and he began to lose weight and strength. Another chest roentgenogram was taken, a definite diagnosis of tuberculosis was made, and the patient was referred to one of the present writers (E S).

The significant findings noted on the first examination (July 18, 1939) were harsh breathing over the left lung anteriorly and coarse râles posteriorly in the interscapular region. The left lung was clear. The heart was entirely negative. Blood

pressure was 110 mm Hg systolic and 70 mm diastolic. The spleen was not enlarged. Temperature was 99.5° F.

Laboratory Data July 31, 1939. The blood count showed hemoglobin, 85 per cent, red blood cells, 4,500,000 per cu mm, white blood cells, 14,200 with polymorphonuclears, 68 per cent, lymphocytes, 20 per cent, eosinophiles, 11 per cent and basophiles, 1 per cent. On August 21, 1939, the blood count showed hemoglobin, 80

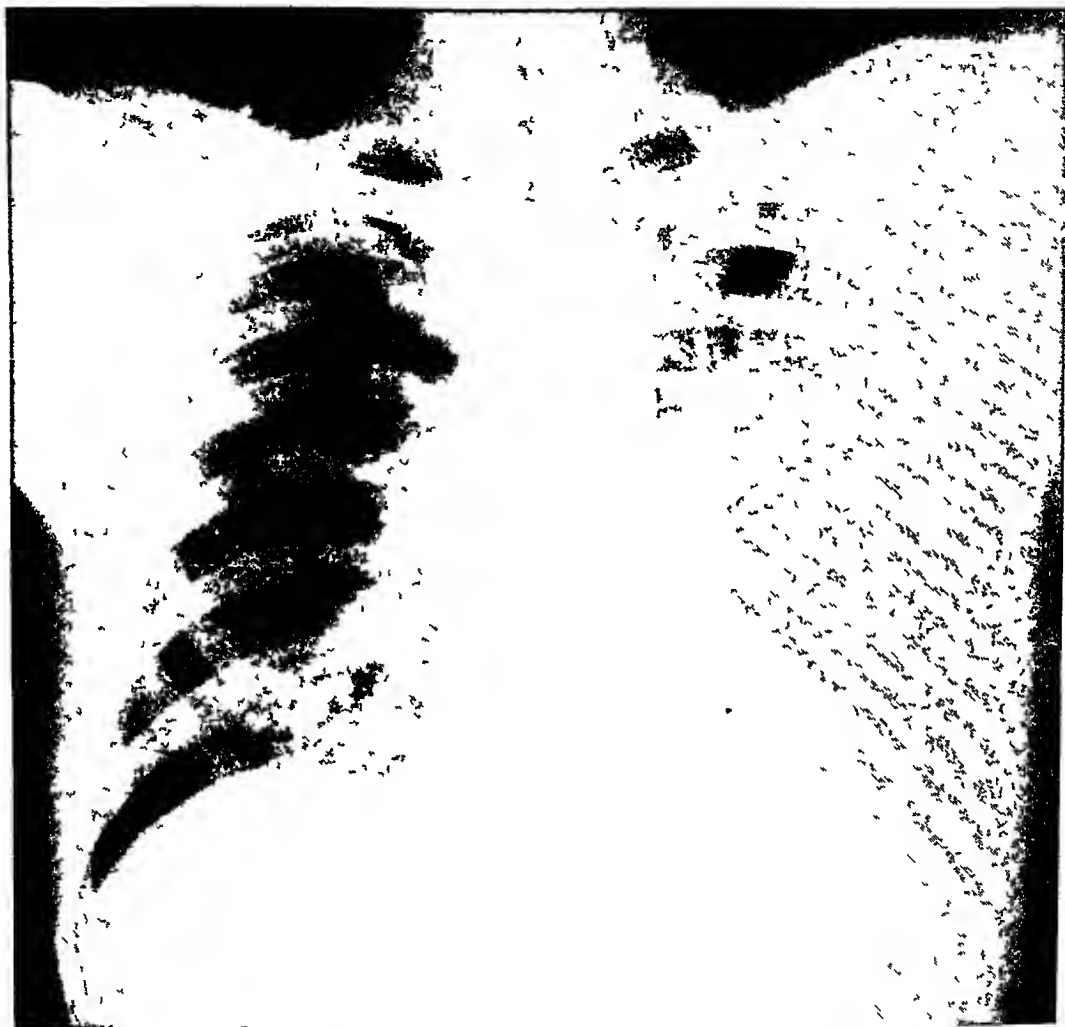


FIG 11 (Case 5) Roentgenogram taken July 31, 1939. Complete clearing of the infiltration in the right lung. Scattered infiltration throughout the left lung.

per cent, red blood cells, 4,650,000, white blood cells, 12,600 with polymorphonuclears 64 per cent, lymphocytes, 21 per cent and eosinophiles, 15 per cent. Another blood count on October 23, 1939, showed hemoglobin, 85 per cent, red blood cells, 5,100,000, white blood cells, 8,500 with polymorphonuclears, 76 per cent, lymphocytes, 19 per cent, monocytes, 2 per cent, eosinophiles, 2 per cent and basophiles, 1 per cent. A number of sputum examinations, including several of concentrated sputum, did not reveal the presence of tubercle bacilli. A search for fungi and spirochetes in the sputum gave negative results. A stool examination failed to show the presence of ascaris larvae.

Roentgenograms A chest roentgenogram (figure 10), taken on May 31, 1939, showed dense infiltration involving almost the entire right lung. There was increase in lung markings throughout the left lung. On July 31, 1939, the chest roentgenogram (figure 11) showed almost complete clearing of the infiltration in the right lung field, but the left lung showed scattered infiltration throughout the lung field. Another chest roentgenogram (figure 12), taken on August 18, 1939, showed some clearing



FIG 12 (Case 5) Roentgenogram taken August 18, 1939. Considerable clearing of the infiltration throughout the left lung. Reappearance of infiltration in the right lung.

of the infiltration throughout the left lung field. In the right lung, however, scattered infiltration throughout the lung, particularly in the second interspace, had reappeared. On September 15, 1939, a chest roentgenogram (figure 13) showed relatively little change in the right lung as compared with the previous film. In the upper half of the left lung field there was now evidence of dense infiltration. On September 29, 1939 the chest roentgenogram (figure 14) showed complete clearing of the infiltration in both lung fields. Chest roentgenograms taken on October 23, 1939, and January 20, 1940, showed no change from the film taken on September 29, 1939, no abnormal changes were noted.

Course July 31, 1939. Temperature was elevated, occasionally as high as 101° F. The cough became spasmodic in character and the patient experienced difficulty in raising sputum. He complained of pain over the right side of his chest.

Examination revealed moist râles and rhonchi throughout the left lung, there were a few râles in the right lung. The patient was seen again on August 21, 1939, after two weeks' rest in the country. The temperature remained elevated, frequently to 101.4° F. There was a slight cough productive of scanty, odorless expectoration. He had no wheezing or asthmatic attacks but complained of a sense of oppression over the front of the chest. The râles and rhonchi had disappeared. He reported

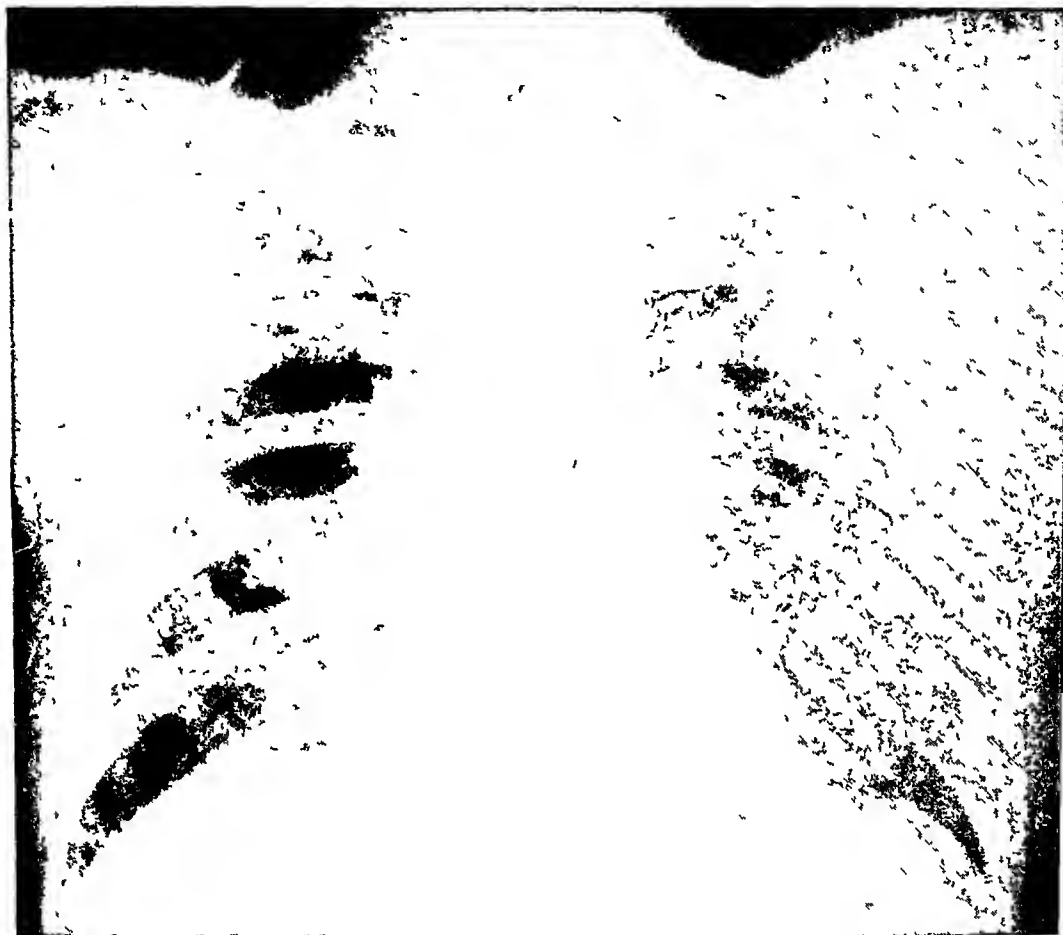


FIG 13 (Case 5) Roentgenogram taken September 15, 1939. Right lung relatively unchanged. Reappearance of dense infiltration in the left upper lobe.

again for examination on September 1, 1939. Except for a slight unproductive cough the patient was symptomless. He had gained four and one-half pounds in weight. Physical examination of the chest was entirely negative. On September 15, 1939, he had no complaints. He had gained five more pounds in weight. There were no abnormal physical findings. September 22, 1939. The patient continued to gain in weight. There was some edema of the left eyelid and supraorbital region which was thought to be due to some allergic manifestation. Otherwise, the physical examination was entirely negative and the patient was symptomless. October 23, 1939, the edema of the left eyelid had disappeared. Abnormal physical findings were absent and the patient claimed that he felt well. The patient returned for routine examinations in November 1939, January 1940, and was last seen in June 1940. He had returned to work in October 1939. He continued to gain weight and had no complaints. Physical examination remained negative.

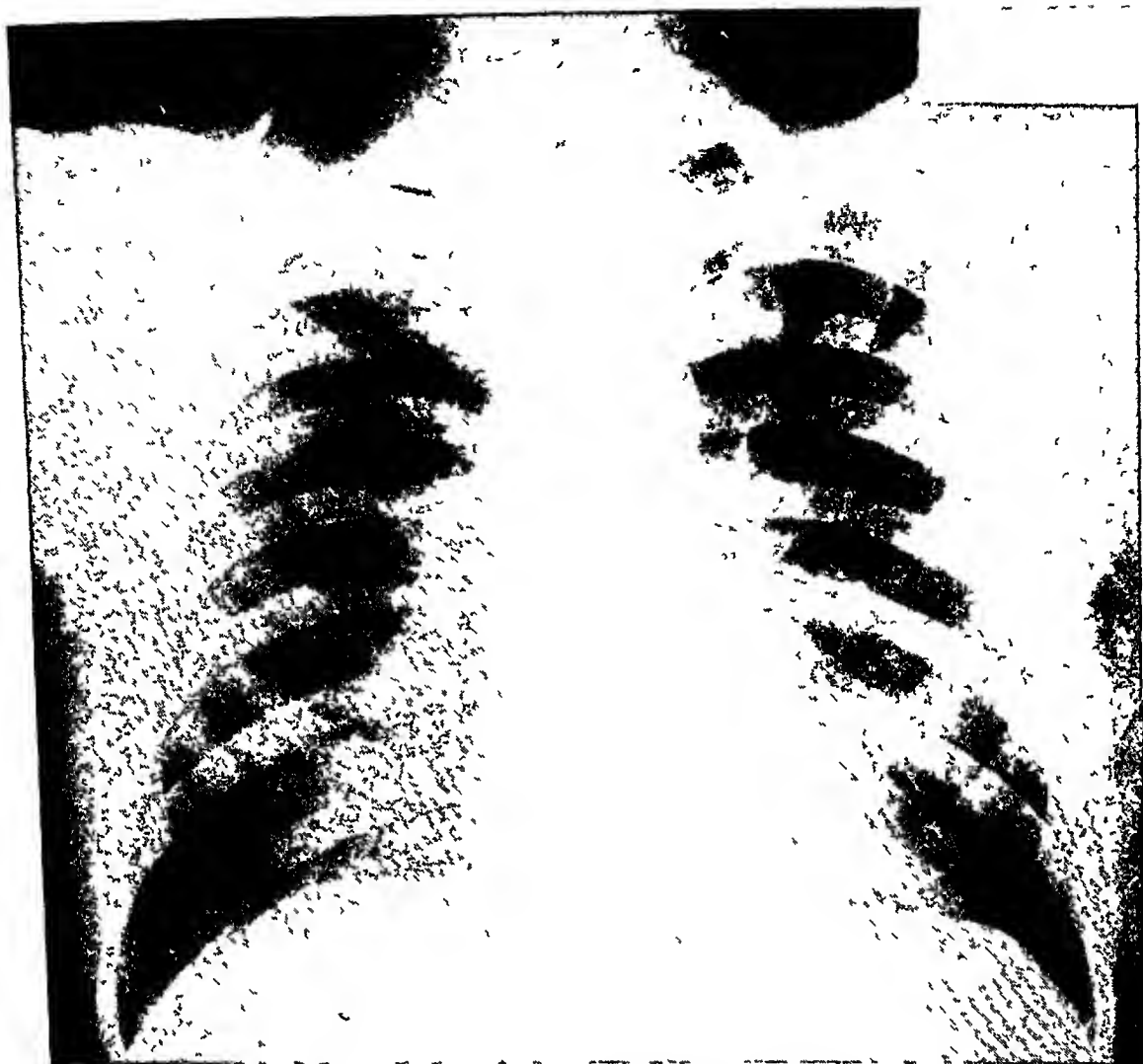


FIG 14 (Case 5) Roentgenogram taken September 29, 1939 Both lung fields clear

Comment This case presents an interesting clinical picture of transitory, migratory pulmonary infiltrations associated with eosinophilia. Except for the absence of cardiac manifestations and the migratory character of the pulmonary infiltrations there is a close similarity between this case and the first one presented. The infiltrations in both instances were not of a tuberculous nature. It is believed that the pulmonary manifestations in these two cases were on an allergic basis.

DISCUSSION

Cases 2 and 3 presented chest roentgenograms indistinguishable from roentgen pictures of pulmonary tuberculosis. Both patients had bronchopneumonia, probably caused by a filtrable virus. During the past several winters such cases have been not uncommonly observed. The roentgenogram at the onset of the illness, the symptoms and blood picture closely simulate the exudative type of tuberculosis. In order to arrive at a definite diagnosis, before instituting collapse therapy, it is wise, therefore, to take

serial chest roentgenograms and make a thorough search for tubercle bacilli in the sputum and aspirated gastric contents

Although the diagnosis in case number 4 was not definitely established, the infiltration and rarefaction seen on the first roentgenogram (figure 8) were thought to be due to lobular atelectasis with beginning pulmonary necrosis as a sequence of bronchial obstruction. Similar roentgenograms which not infrequently need to be differentiated from pulmonary tuberculosis are seen in cases of pulmonary neoplasms and lung abscess. Bronchoscopic examination, serial roentgenograms and absence of tubercle bacilli disclose the non-tuberculous nature of the pathologic bronchopulmonary process.

Cases 1 and 5 present interesting problems in pathogenesis. In connection with these cases it is of interest to refer to reports by Smith,³ Muller,⁴ and Löffler,^{5,6} who described similar cases, and to review the latter report by Löffler in some detail. In 1936 he reported 51 instances of patients with transitory pulmonary infiltrations associated with eosinophilia in every case. The roentgenograms presented various types of densities described as follows: (1) large, more or less irregularly outlined densities which were unilateral or bilateral, (2) small infraclavicular infiltrations of the type described by Assmann, (3) multiple unilateral or bilateral circular densities, (4) sharply defined densities situated in the right middle lobe, (5) infiltrations indistinguishable from the adult-type of pulmonary tuberculosis. In the differential leukocyte count the number of eosinophiles ranged between 10 and 50 per cent. In some instances the eosinophilia reached a peak when the pulmonary infiltration had almost entirely cleared. Eosinophilia persisted for some time in some of the cases. There was no strict parallelism between the extent of the eosinophilia and the pulmonary infiltration. Some of the patients who had blood counts prior to the appearance of the pulmonary infiltrations showed no eosinophilia. Occasionally there was a leukocytosis up to 15,000 white blood cells. The sedimentation rate as a rule ranged between 8-15 mm in one hour, in a few cases a more rapid rate was observed. Constitutional symptoms were mild or entirely absent. The clinical course was very benign, and the infiltrations on the roentgenograms cleared in three to eight days. In only one instance did pulmonary infiltration reappear, and that occurred one year after the original episode. Sputum specimens of all the patients were examined for tubercle bacilli with negative results in every case. All the patients were adults and most of the cases occurred during the months of July and August. In two instances the condition was noted in members of the same family. In 37 cases the tuberculin reaction was positive and in 13 instances a negative reaction was obtained.

Löffler discusses the pathogenesis of this clinical entity. He rules out pulmonary embolism with infarction, pneumonia, bronchial asthma with partial atelectasis, and pulmonary tuberculosis. He considered ascariasis as the etiology, but examination of the sputum and stools did not disclose the presence of ascaris larvae in a single instance. Löffler thinks that the

pathogenesis in these cases is similar to erythema nodosum, the lung reacts with an inflammatory exudate to a toxin. It is his impression that the pulmonary manifestation is on an allergic basis.

Cases 1 and 5 described by the present authors can be grouped with the clinical entity described by Löffler. Both patients had transitory pulmonary infiltrations associated with eosinophilia. The clinical picture in these two instances differed in some respects from the majority of cases in Löffler's series. The symptoms in the present cases were more pronounced and persisted for longer periods of time. The pulmonary infiltrations observed on the serial roentgenograms showed less rapid clearing, and in case 5 the infiltrations were of a peculiarly migratory character. However, it is suggested that the differences can be explained logically on the basis of a more intense and prolonged allergic response to some allergen. The agent producing the allergic reaction in the two cases presented was not determined. It should also be pointed out that Löffler did not observe cardiac manifestations in any of his patients, at any rate, he makes no mention of them. In case 1 there was evidence of right-sided cardiac strain. Here again, it can reasonably be assumed that because of the more pronounced allergic reaction the pulmonary exudate persisted for a sufficient length of time to produce increased resistance in the pulmonary circulation resulting in right ventricular strain. With the absorption of the pulmonary exudate the heart returned to normal size.

SUMMARY AND CONCLUSIONS

- 1 Five cases of non-tuberculous pulmonary disease mistaken for pulmonary tuberculosis are presented.
- 2 Reliance on a single chest roentgenogram for diagnosis frequently leads to error.
- 3 When tubercle bacilli cannot be found in the sputum or aspirated gastric contents by all methods of examination, including cultures and guinea pig inoculation, it is extremely unlikely that the bronchopulmonary disease is of tuberculous etiology.
- 4 The clinical picture and pathogenesis of pulmonary infiltrations associated with eosinophilia are discussed.

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CASE REPORTS

INTRATHORACIC LIPOMA; A CASE REPORT *

By OSCAR SWINEFORD, JR., M.D., F.A.C.P., and CHARLES J.
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THE subject of intrathoracic neoplasms has been reviewed recently by Heuer and his associates ^{1,3}. They summarized all case reports to date. McCorkle, Koerth, and Donaldson ² tabulated the most common symptoms and signs of the cases of thoracic lipomata of each type reported before 1938.

The following case of intrathoracic lipoma is reported because it is the second in which asthma was the chief complaint,² and because it is the eighth largest of the 25 wholly intrathoracic lipomata now on record.

CASE REPORT

A 62 year old white single male was admitted in severe status asthmaticus and congestive failure of 10 days' duration.

Present Illness A transient acute respiratory infection had precipitated an attack of asthma, which was followed promptly by congestive failure. He had had to sit up in a chair for 96 hours prior to admission.

Systems History The patient had had asthma for 25 years, usually precipitated by acute respiratory infections to which he was unduly susceptible. In October 1937, he was bronchoscoped by Dr. Porter Vinson of Richmond, Virginia, with marked relief of a severe episode of asthma until April 1939, when he had to be bronchoscoped a second time. He was markedly, but not completely, relieved again until two weeks before admission. Bilateral bronchospasm with moderate serous secretion, but no bronchostenosis, was noted both times.

He had had palpitation for 10 years, hypertension for eight years, dyspnea on exertion for five years, orthopnea for four years, and an anginal attack two years before admission. He had had a few convulsions since 1935. He had had no congestive failure until his final illness.

Other symptoms were irrelevant.

Physical Examination The patient was having severe asthma. He was cyanotic. There were signs of moderate congestive failure. In the base of the right lung there were dullness and markedly diminished intensity of tactile fremitus and of the voice and breath sounds. The heart seemed slightly enlarged to the left. There was moderate arteriosclerosis of the peripheral and retinal arteries. His venous pressure was 170 mm of water. His blood pressure was 170 mm Hg systolic and 90 mm diastolic. Other physical findings were irrelevant.

Course in Hospital Adrenalin, caffeine, seconal, mercupurin and theamin relieved his alarming acute symptoms. He was digitalized. His venous pressure became normal. His blood pressure dropped to 160 mm Hg systolic and 75 mm diastolic, but he continued to have moderately severe asthma.

* Received for publication December 2, 1940.

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On the fourth day he had a Jacksonian convulsion. The aura were twitching of the left arm and jerking of his head to the left.

He was bronchoscoped on the sixth day. Thick tenacious secretion was aspirated from the trachea and the bronchi. The bronchi appeared partially collapsed. The orifice of the right middle lobe bronchus was dimpled and narrowed to about 2 mm.

He had a severe attack of asthma, with shock, immediately after the bronchoscopy. He remained semicomatose with frequent periods of Cheyne-Stokes respiration, cyanosis, and pulmonary edema for six days, when he died.

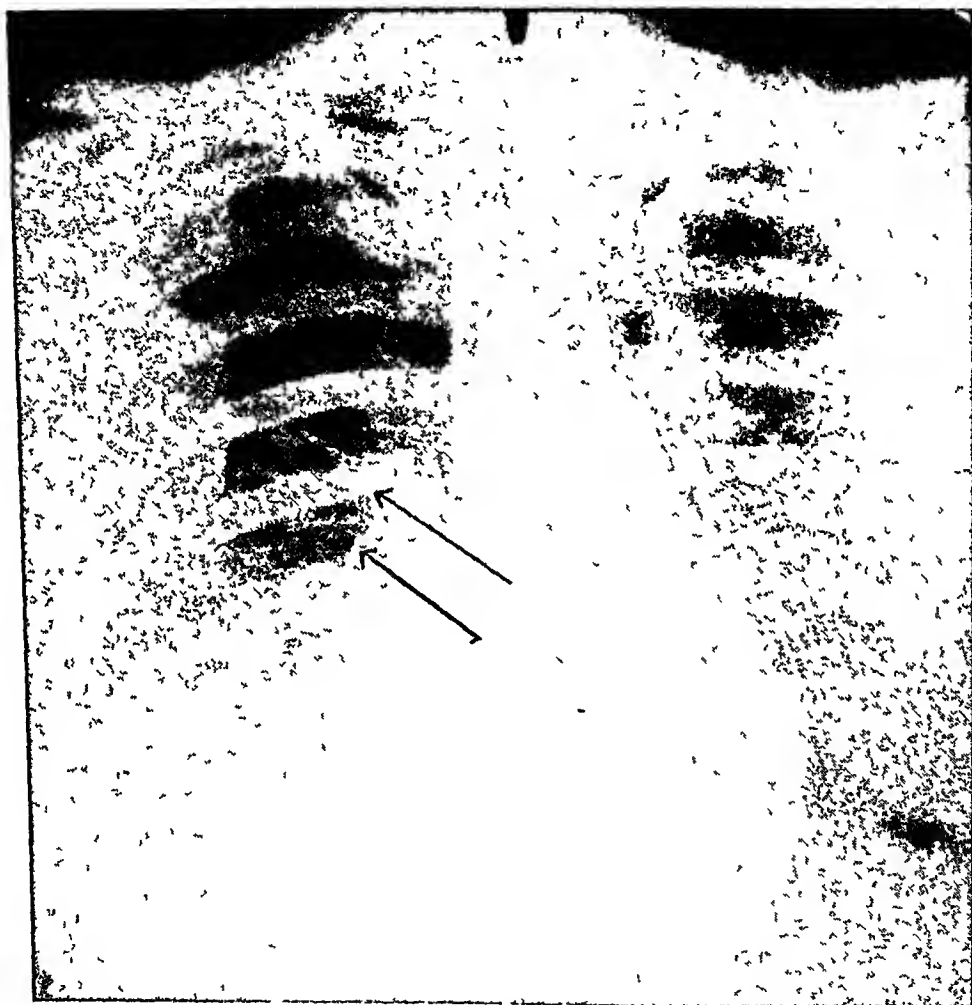


FIG 1 October 5, 1937 (Dr Fred Hodges, Richmond, Virginia, Roentgenologist) Note two rounded masses in the right hilar zone and the apparent elevation of the right diaphragm, with decreasing density of the shadow from the midclavicular line to the periphery.

Special Examinations *Staphylococcus albus non-hemolyticus*, a chromogenic micrococcus, and *Streptococcus viridans* were cultured from the sputum. The electrocardiogram showed evidence of myocardial damage. No significant abnormalities were noted in routine examinations of the urine, blood urea, hemoglobin, red and white blood cells, blood smear, blood Wassermann and Kahn tests, and roentgenograms of the sinuses.

The roentgen-ray examinations of the chest were most interesting. Dr Fred Hodges of Richmond, Virginia, in October 1937 had reported (figure 1) "The left side is negative except for very broad hilum shadows. On the right side the dia-

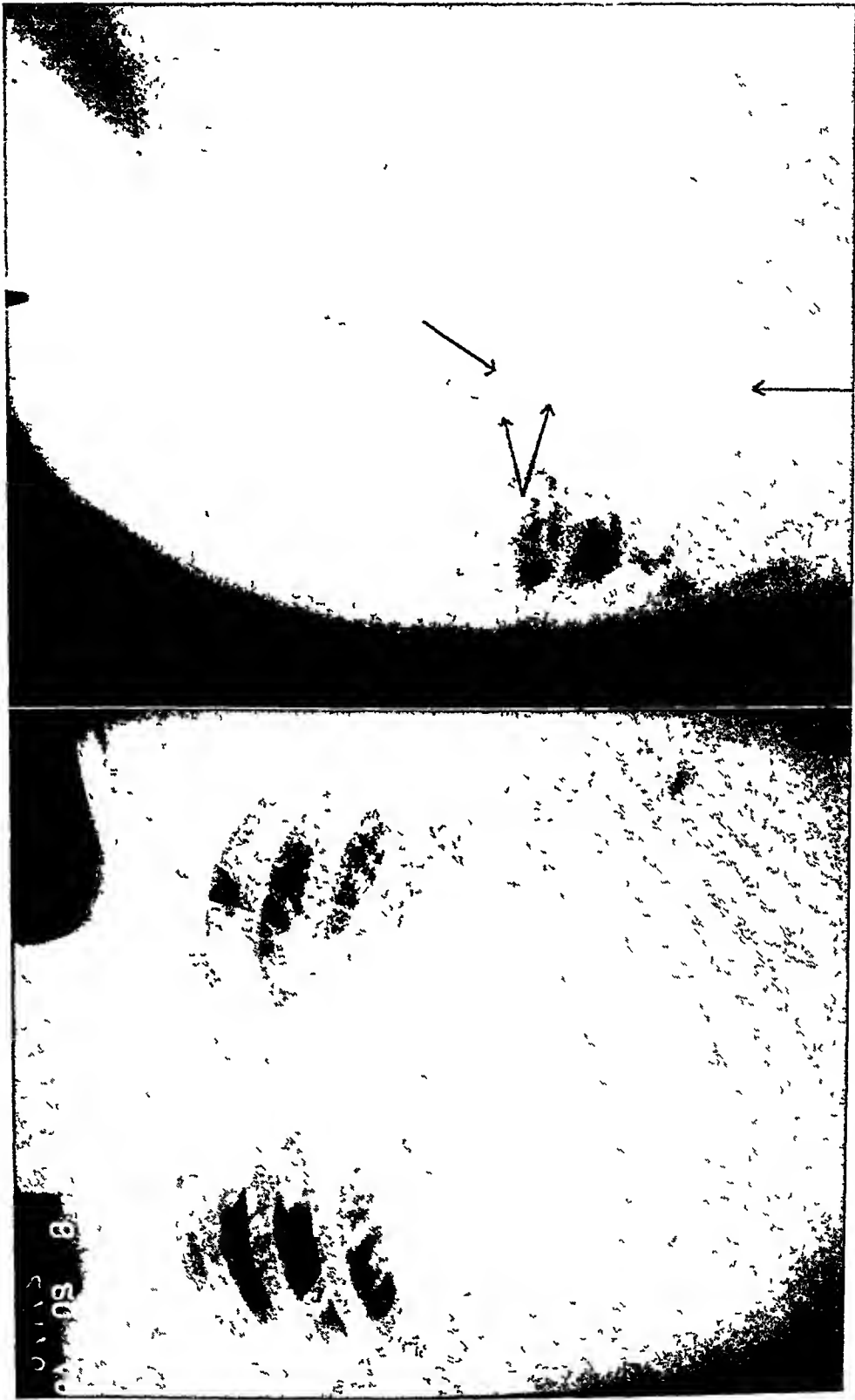


FIG 2 August 20, 1940 The anterior-posterior films show a marked interim increase in the size of the tumor shadow, without the decreasing density from the center to the periphery noted in figure 1. The lateral view shows atelectasis of the middle lobe and an irregular upper border of the tumor. Note the atelectasis extending below the upper border of the tumor. Both are on the right. This should have suggested a mass lesion and not an elevated diaphragm.

phragm is elevated There are two masses at the hilum, the larger being about 3 cm in diameter The changes should be due to atelectasis or possibly a growth at the hilum "

Dr Vincent Archer, University, Virginia, interpreted films (figure 2) taken during the final illness as follows "Marked opacity in the right base up to the level of the fourth rib anteriorly There is an accentuation of the lung markings throughout



FIG 3 The lipoma in its relation to the liver, heart and lungs Note the narrow, collapsed, pale middle lobe The upper and lower lobes are compressed also

both lungs with calcium deposits in the left hilus zone A lateral view shows the diaphragm elevated anteriorly mainly There is thought to be definite atelectasis of the middle lobe which probably accounts for at least part of the elevation and the density of the right base The lung markings running into the right upper were quite markedly accentuated in the lateral view "

Postmortem examination showed a large lipoma filling the base of the right thorax (figure 3) It was free except for a filmy attachment to the right mediastinal pleura It weighed 2310 grams Its longest diameter was 26 cm The right lung was

displaced upward. The middle lobe was completely atelectatic. It was unpigmented, suggesting non-function of long standing. The orifice of the middle lobe bronchus was marked only by a small dimple. About one-third of the right lower lobe was atelectatic. In both lungs there was patchy consolidation with mucopurulent material in the bronchi. The left lung was emphysematous and covered with old adhesions. The mediastinum was not displaced. The heart weighed 550 grams. Both ventricles were slightly hypertrophied but not dilated. There was no chronic passive congestion. There was some pulmonary and peripheral arteriosclerosis. Microscopic examination of the tissues added nothing. Other findings were irrelevant.

DISCUSSION

It is not necessary to assume that the lipoma was a primary cause of the asthma. Such marked relief, twice, from bronchoscopy would be hard to reconcile with this assumption. Besides, he had had asthma for many years whenever he had acute respiratory infections. Then, too, bronchial stenosis is a well recognized cause of asthma. The stenosis of the middle lobe bronchus in this case was apparently inflammatory in origin and not from direct external pressure. The absence of pigment, suggesting long standing absence of middle lobe function, further complicates the interpretation of the rôle of the lipoma as a cause of the asthma. It is interesting to point out, however, that McCorkle, Koerth, and Donaldson described signs or symptoms of asthma of some degree in five of the 19 cases which they reviewed, although they did not use the term asthma except in their own case.²

A review of the roentgenograms (figure 2) of the chest during the final illness suggests the presence of a mass above the diaphragm. They do not, however, have the one feature suggestive of an intrathoracic lipoma, namely, diminishing density of the shadow from the center toward the periphery. This feature was present to some degree in the films taken in 1937 (figure 1).

SUMMARY

This is the twenty-fifth report of a wholly intrathoracic lipoma. It was not diagnosed clinically. Asthma was the chief complaint. Relevant postmortem findings are presented.

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BENIGN HEPATOMA; REVIEW OF THE LITERATURE AND REPORT OF A CASE¹

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LOCAL hyperplastic processes of the liver may manifest themselves variously in the form of a solitary focus of congenital origin in a normal liver, as multiple nodular hyperplasia, or in the guise either of a solitary or multiple adenomata. All these pathological conditions may occur indiscriminately with or without concomitant cirrhosis. Occasionally, benign tumors resulting from simple hypertrophy may eventually assume a malignant character.

In a dissertation submitted in 1910, Monier-Vinard¹ described a so-called new type of primary tumor of the liver, for which he proposed the specific and exclusive title of hepatoma. The latter he defined as a benign neoplasm of the hepatic parenchyma arising chiefly from liver-cord cells, ordinarily single but sometimes multiple, and most common in adults. This designation was suggested as a substitute for the less exact terms of adenoma of the liver and multinodular hyperplasia employed by previous writers on the subject.

However, at present considerable confusion exists concerning the appropriate use of the expression *hepatoma*. For example, primary epithelial tumors of the liver are correctly designated by Swalm and Morrison² as hepatomata when they are derived from liver cells, and as cholangiomata when they originate from intrahepatic bile-duct cells. A third group which arise from both liver cells and bile-duct cells they denominate mixed tumors. On the contrary, Ewing³ includes under the classification of hepatoma, the benign form, adenoma, and the malignant forms, adenocarcinoma and carcinoma of the liver.

Solitary adenomata derived from liver cells are seldom observed, and their clinical differentiation from cholecystitis and lithiasis is often difficult. Although they are believed by some authorities to be of congenital origin, it is also regarded as probable that acquired lesions may occasion neoplastic overgrowth of isolated portions of the liver. Multiple adenomata involve a hyperplasia of liver cells and frequently are accompanied by a cirrhosis which dominates the clinical picture. The important rôle assumed by cirrhosis in the etiology of these latter tumors is ascribed to the compensatory hyperplasia induced by the antecedent hepatic stasis. This occurs quite commonly and produces these multiple adenomata of cirrhosis. Certain solitary tumors of the liver are thought to be due to interference with the supply of blood to the organ.

In typical solitary adenoma the veins are not invaded, and its benign character is attributable to its encapsulation. The transitional forms intermediate between adenoma and adenocarcinoma are distinguished chiefly by invasion of the veins, gradual progression beyond their capsule, and multiplication of tumors. The primary tumor generally consists of cords, tubes, and alveoli markedly resembling the structure of the liver. In occasional instances all three of these elements are encountered in a single tumor. Very often the neoplasm contains strands of cells which it is difficult to differentiate microscopically from the normal tissue. The cells are granular and acidophile, or very fatty. The stroma is composed mainly of capillaries.

* Received for publication January 13, 1941.

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Benign tumors of the liver rarely exhibit symptoms unless they become sufficiently voluminous to cause mechanical pressure within the organ itself or upon the adjacent structures. The concomitant ascites, hematemesis, and thrombosis of the portal vein which are observed are related to the associated cirrhosis. Because of their failure to present a definite clinical syndrome, non-malignant hepatic tumors are usually discovered either by accident during the life of the patient or else only at autopsy.



FIG 1 Flat plate of abdomen showing shadow of tumor

Unless they are large and productive of a considerable degree of discomfort, benign tumors of the liver seldom require treatment. Nevertheless, as in all cases of abdominal tumor, if there is even the slightest doubt concerning the diagnosis, an exploratory operation is always recommended in order to exclude the possibility of malignancy.

The purpose of the present communication is to record a case of true benign hepatoma and to include also a brief survey of those previously published. The comparative infrequency of benign tumors of the liver is attested by the fact that apparently only 58 cases have thus far been reported in the medical literature of the entire world. In 1908, Keller⁴ presented a comprehensive tabular summary of the available data in the 55 cases contributed during the preceding

half century under the general title of adenoma. Among the patients comprised in this group, the youngest was a female aged nine, and the eldest a male of 80. Cirrhosis of the liver was present in 10 instances. In 18 the tumors were multiple, whereas in six the hepatoma was solitary. Encapsulation was complete in three and partial in eight. Clinical symptoms of obstruction of the portal circulation with ascites were noted in 11 cases, all of which terminated fatally within a few months following the onset of intense icterus, splenic tumor, and progressive marasmus. Similar symptoms were observed in two other instances in which death occurred after a period of illness ranging from several months to about one year.

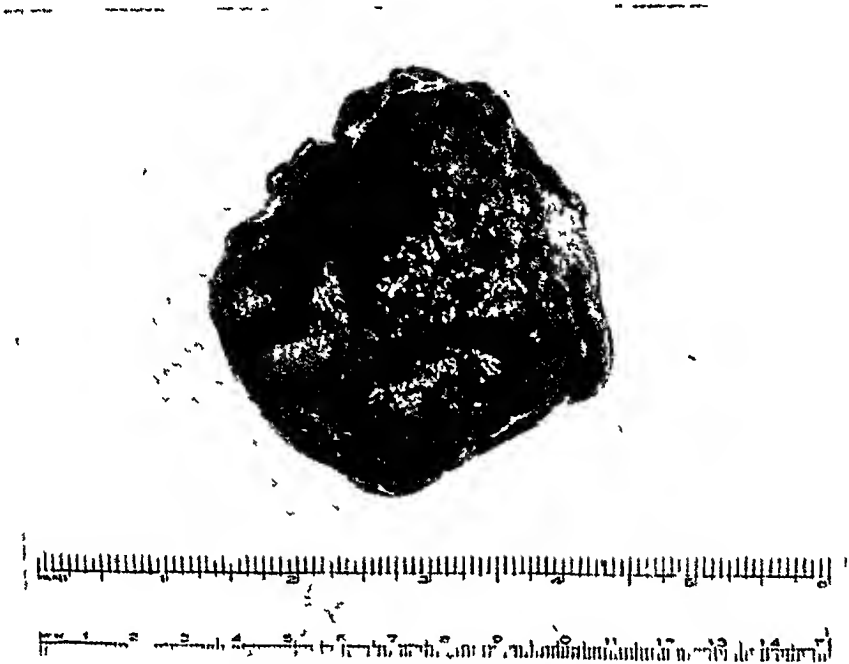


FIG 2 Mass removed at operation

Monier-Vinard¹ in 1910 reported a classic case of benign hepatoma in a man of 54, with a history of chronic alcoholism of from 20 to 30 years' duration, and clinical symptoms of dyspepsia, emesis, diarrhea, and aversion toward solid foods.

For several months prior to consultation the patient had remarked a progressive increase in volume of the abdomen. At the time of admission to the hospital he complained of extreme debility and of pain in the upper abdominal region, especially after meals. On physical examination the abdomen appeared greatly enlarged. The spleen was palpable over an area approximately equivalent in extent to the palm of the hand. Palpation in the hepatic region revealed upon the surface of the liver very numerous and extremely hard irregularities which suggested the diagnosis of simple cirrhosis or the possibility of a secondary neoplasia of the liver. No sugar and only slight traces of albumin were found on urinalysis. A considerable augmentation of the ascites was noted upon the second day following admission, with a corresponding increase in the size of the abdomen. Fourteen liters of blood-stained fluid, which subsequently yielded an abundant precipitate of red corpuscles, were evacuated by puncture.

Two weeks later the patient was attacked by violent colic and passed about half a liter of extremely fetid, reddish brown diarrheal matter composed of what proved on microscopic examination to consist of greatly altered red corpuscles. On the day after this intestinal hemorrhage a recent disseminated purpuric eruption was observed, particularly upon the lower limbs and over the trunk and upper members. During the week which followed, the general condition of the patient became aggravated, primarily in consequence of an exceedingly copious intestinal hemorrhage. Four days later death occurred in progressive coma.

Microscopic examination of the liver showed that the latter was the seat of a cirrhosis and of a neoplasm whose cells presented the characteristic arrangements of cords and strands of from two to three cells in thickness, and of nests of cells

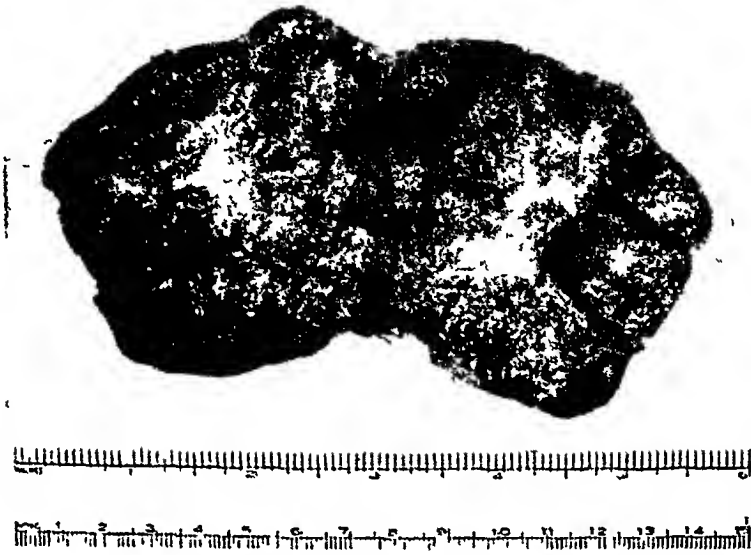


FIG 3 Tumor cut open to show gross appearance of tissue

that simulated the formation of acini. The tumor cells resembled liver cells in their cytoplasm and in the size of their nucleus but were more hyperchromatic, and some of them were in a state of active mitosis. An epithelial type of cell with a large amount of cytoplasm and giant cells of epithelial origin, likewise abundantly supplied with cytoplasm, were also encountered. The entire tumor presented a highly vascular aspect, the newly formed capillaries which pervaded the section exhibiting the appearance of granulation tissue. The stroma consisted of partly degenerated connective tissue. Along the margin of the tumor there was a clearly defined capsule of connective tissue.

The etiology of hepatoma was attributed by Monier-Vinard¹ to chronic inflammatory irritation coexistent with cirrhosis. He classified hepatoma as the prototype of a new group of tumors which might be described by the term *organomas*. This group appeared to him to be represented by myeloid leukemia and lymphoid leukemia, and to include also tumors which developed in organs or tissues derived from the mesoderm.

A rare instance of the occurrence of a solitary liver-cell adenoma or hepatoma in childhood was recorded in 1923 by Shaw.⁵

Ten days prior to admission to hospital, a boy aged 13 was attacked suddenly by severe abdominal pain, followed by the appearance of a swelling in his right side, the pain having persisted, though with diminishing intensity, until the fourth day preceding admission. Physical examination revealed in the right hypochondrium a large nodular swelling apparently continuous with the liver and the right kidney. Laparotomy was performed, and a large lobulated tumor was found to occupy a considerable proportion of the right lobe of the liver. The rest of the liver appeared normal, with no cirrhosis, no secondary deposits in the peritoneal sac, and no ascites. The tumor was removed together with the attached gall-bladder. Recovery was uneventful, and the patient was discharged three weeks after the operation.

The surface of the tumor was covered only by the distended capsule of the liver. Its upper surface was rendered irregular by deep branching furrows, whereas the lobules upon its anterior surface were separated by sharp depressions, one of which divided this portion of the tumor into two parts. From a central area of fibrosis numerous broad strands of connective tissue radiated outwards, gradually became thinner, and finally disappeared near the periphery, which was more markedly cellular in aspect than the glistening fibrous center. A few scattered blood vessels which showed no thrombosis were seen in the fibrous strands, but no bile ducts were discerned. At the junction of the nodular portion with the principal mass of the neoplasm there were several opaque, white, soft, circumscribed areas of tumor tissue, which were highly cellular, devoid of bile staining, and encapsulated by fibrous tissue. The posterior and lateral margins of the neoplasm presented a clearly defined edge but were not encapsulated. The adjacent hepatic tissue was fatty and slightly compressed, but there was no evidence of cirrhosis, no thrombi in vessels, and no bile staining. The gall-bladder was normal.

Microscopic examination of a part taken from the right posterior region of the growth showed that numerous broad strands of fibrous tissue separated the tumor cells into masses of irregular size and shape, this dense, rather hyaline stroma containing comparatively few cells. Thinner and more delicate strands arose from the principal bands and passed into the parenchyma. Although some of the neoplastic cells resembled those of normal liver in size, shape, and general structure, the majority were quite atypical, with a large, round, oval, or lobulated nucleus, thicker nuclear membrane, and a nucleolus (occasionally multiple) larger than in the normal liver cell. Many of the nuclei were hyperchromatic, and others were markedly altered by nuclear vacuolation. Multiplication apparently occurred somewhat by direct division, and mitotic figures were scanty. The cytoplasm exhibited wide variation with respect to staining capacities in the individual cells. A certain proportion of cells formed bile in the form of green granules or blocks within the protoplasm.

Portions taken from several other parts of the tumor for examination presented generally a similar histological structure, except for the circumscribed soft area from the junction of the nodular part of the tumor with the main growth, which was in marked contrast to all other parts examined. It consisted of strands of cells arranged in a distinctly trabecular formation which resembled more closely the adenomatous type seen in the hyperplastic nodules of cirrhosis than the normal liver. The tissue was distinctly vascular, and a network of branching capillaries passed between the trabeculae. There was very little fibrous tissue. The tumor cells bore a striking resemblance to normal liver cells but were somewhat larger, though fairly uniform in size and shape. The nucleus was larger, the nucleolus more prominent, and the cytoplasm less granular and more chromophilic. Cells with two or more nuclei were exceedingly rare. Intercellular canaliculi were common but contained no bile. The cells lay close to the capillaries, but there was no invasion of the larger vessels in the stroma. Mitotic figures were rare. There was no formation of bile and no bile

ducts. Nuclear vacuolation and hydropic degeneration were virtually absent, but some cells contained small round hyaline bodies in their cytoplasm.

The presumption of the origin of the tumor from liver cells was thus confirmed by the appearance of the neoplastic cells, their capacity to form bile, and their trabecular arrangement in places. The neoplasm was regarded as a typical example of the rare group of tumors of the liver which are characterized by occurrence in infancy or childhood, the presence of a solitary growth, and the

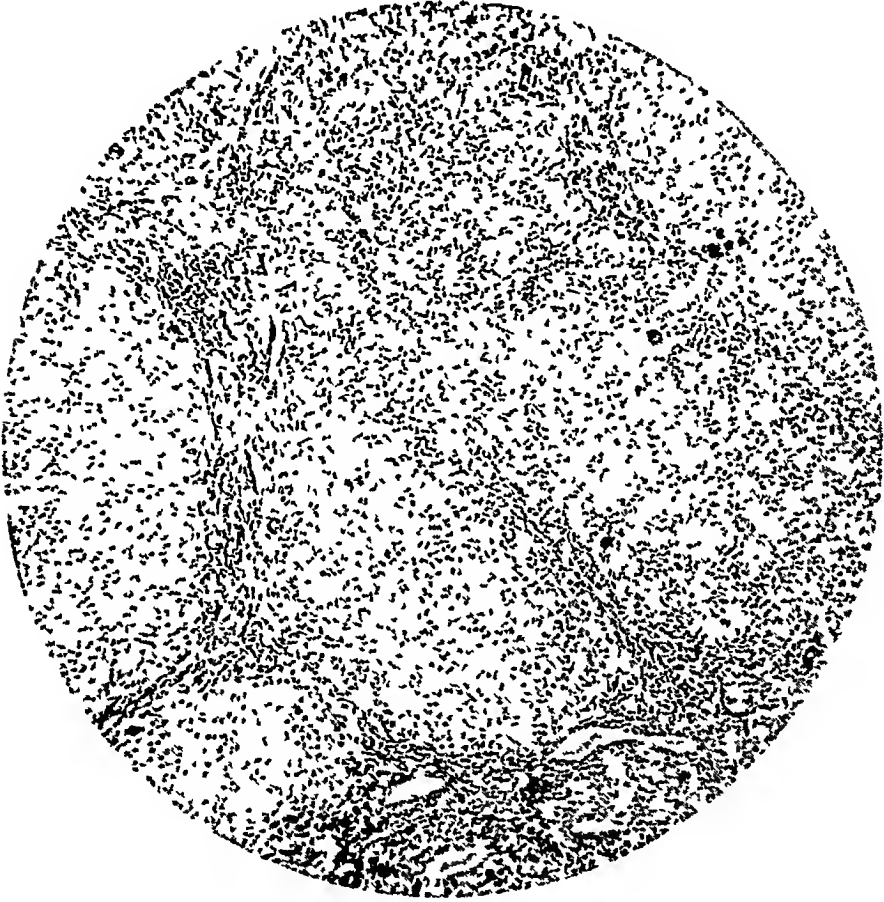


FIG 4 Photomicrograph of section of tumor

absence of cirrhosis or other associated pathological alteration which might explain an initial hyperplasia of liver cells. There was no evidence whatever of a development from epithelium of the bile ducts. Genesis of the tumor from a cell-nest of congenital origin was also considered as a possibility in the case under consideration.

More recently an extraordinary case of hepatoma with recurrence five years after the original operation was reported by Glennon and Byrne ⁶

At the time of admission to hospital the patient, a man aged 49, suffered from pain in the right upper quadrant of the abdomen and in the region of the left kidney,

and from eructation. The onset of pain and digestive disturbance dated from a fall sustained eight years previously, when four ribs on the right side were fractured. Since then the pain had been practically constant but in nowise associated with the ingestion of food. Loss of weight had been considerable. On examination it was observed that the abdomen was somewhat distended, particularly on the right side, and that a fairly large, soft, slightly tender mass apparently connected with the liver extended downward almost to the umbilicus and backward toward the right kidney. The mass was smooth, fluctuant, and regular in outline. Fluoroscopic and radiographic studies of the gastrointestinal tract proved negative. Exploratory laparotomy disclosed on the left lobe of the liver a mass the size of a large grapefruit, entirely free from adhesions, and of grayish color. A number of blood vessels were seen in the wall of the mass. Except for this mass the liver was, like the gall-bladder, normal. An incision into the most prominent part of the mass revealed a soft, grayish tissue evidently in process of degeneration. At this juncture profuse bleeding from the wall of the mass necessitated the insertion of a large pack into the cavity, the contents of which were thereupon removed, and the wound was closed with the pack protruding from its upper angle. Following immediate microscopic examination the tumor was declared malignant. Loss of the disintegrated mass removed as described rendered subsequent microscopic study impossible. Despite the unfavorable prognosis, healing of the wound and general improvement ensued within a few weeks.

About five years later the patient was again admitted with a recurrence of the tumor, which this time was located in the right upper quadrant of the abdomen and was as large at least as the original growth, but apparently extended superiorly toward the ensiform cartilage. There was simultaneous recurrence of former symptoms of loss of weight, anorexia, and eructation. The abdomen was reopened through the old scar, and a tumor the approximate size of a grapefruit was found arising from the inferior and anterior surfaces of the left lobe of the liver. Adhesions were present between the abdominal wall and the tumor and even denser adhesions between the tumor and the posterior abdominal wall near the median line. The tumor was freed, the left lobe of the liver mobilized, and a complete lobectomy with removal of the attached tumor was performed. Convalescence was uneventful, and the patient was discharged in due course.

After six months of definite improvement, during which the patient remained under constant observation, the tumor reappeared, on this occasion outside the liver in the retroperitoneal region and on the left side of the abdomen. Deep roentgenotherapy of the now inoperable tumor afforded no relief, and death occurred 15 months later with all the phenomena of carcinoma. Autopsy revealed an extensive retroperitoneal mass which compressed the stomach and intestines superiorly and laterally but did not invade these organs. The liver was free from the tumorous growth and exhibited only the old scar of the lobectomy. No metastases were found anywhere.

Macroscopically the tumor removed with the left lobe of the liver was roughly conical in shape and measured 15 centimeters from apex to base, and eight centimeters in diameter, with about four centimeters of normal liver tissue attached to the base. The entire center of the mass consisted of disintegrated necrotic tissue which resembled closely that encountered on examination of the original tumor. Microscopic section showed tissue only moderately cellular, with numerous large and small areas of coagulative necrosis. The cells of the tumor itself, which exactly simulated liver cells in their cytoplasm and the size of their nucleus, exhibited the typical disposition into cords and strands, with clusters of cells highly suggestive of adenocarcinoma. The stroma of connective tissue presented scattered evidences of degeneration. Epithelioid cells with a divided nucleus and giant cells, also of epithelial origin, with a large single hyperchromatic nucleus, all containing large amounts of clear staining cytoplasm, were observed. Vascularization was well marked. The mass removed at autopsy resembled the original tumor macroscopically as well as microscopically.

In the opinion of Glennon and Byrne,⁶ the foregoing facts demonstrate that the tumor in question arose from liver-cord cells, and commenced as a single encapsulated solitary tumor, namely, a hepatoma. Although its histological characteristics apparently identified it as a partly differentiated malignant tumor, encapsulation of the original neoplasm was believed by them to exclude typical malignancy irrespective of the histological picture which was presented.

The paucity of examples of benign hepatoma, as well as the somewhat unusual features presented by the case about to be reported, appeared to afford ample warrant for its publication.

CASE REPORT

A married woman, aged 38, on June 11, 1940, applied for treatment of a mild acute upper respiratory infection. During the course of her conversation the patient remarked that for the past fortnight she had had a sense of consciousness of her right upper abdomen. There was no pain, discomfort, or any other symptoms. On palpating her abdomen she thought she had felt a mass in the right upper quadrant. Apart from the slight discomfort incident to her respiratory infection, she felt quite well. Her appetite was excellent, bowels regular, and sleep sound. She gave a personal history of chronic sinusitis and chronic tonsillitis. Bursitis of the left shoulder with calcification occurred in 1937. Her family history was irrelevant. On January 1, 1940, an uneventful labor had terminated in the delivery of a normal child. There had since been a small increase in weight, which at the time of consultation was slightly above the estimated normal.

Physical examination revealed an alert, young white female of healthy appearance, with normal gait and posture. Height, 61 inches, weight, 135 pounds, temperature, 100° F, pulse, 90, blood pressure, 126 mm Hg systolic and 84 mm diastolic. Pupils were equal, moderately contracted, and reacted to light and during accommodation. Sclerae were clear, and extrinsic movements normal. There was no strabismus and no exophthalmos. Ears were normal. Nasal mucosa was reddened and congested, with a thin mucopurulent discharge. Teeth and gums were normal, and tongue clean. Tonsils were grossly infected, and the pharynx was reddened. The thyroid gland was not enlarged. A few cervical lymphatic glands were palpable. The breasts were of equal size and exhibited no masses or tenderness. Cardiac sounds were normal in intensity, quality, and rhythm, without adventitious sounds. Lungs were clear. Examination of the abdomen proved negative with the patient in the recumbent position. On sitting and standing, the smooth, round lower pole of a mass, which was firm and insensitive to pressure, was palpable in the right upper abdomen just above the level of the umbilicus. The pelvis was within the normal range. Urinalysis and hemogram were negative. Icterus index was 9, basal metabolic rate, —6. Fluoroscopic examination of the chest proved negative. Roentgenographic studies of the gastrointestinal tract and of the gall-bladder (Graham-Cole technic) disclosed no abnormalities. An intravenous pyelogram revealed nothing abnormal. A radiograph of the nasal accessory sinuses showed slight clouding of maxillary sinuses and anterior ethmoids.

All radiographs of the abdomen revealed a mass which occupied the right upper quadrant. Its inferior pole was rounded, but in no wise resembled the lower border of the liver. It was impossible to determine from the films whether the image represented a prolongation of the liver or a separate mass. The patient was referred to Dr. H. H. Kerr of Washington, D. C., for exploratory laparotomy.

On August 5, 1940, under anesthesia with avertin and nitrous oxide, a high right transverse incision was made from above the costal border in the axillary line to the midline above the umbilicus. The fascia of the external oblique muscle was

split in the direction of its fibers, and this incision was carried across the anterior sheath of the rectus. The internal oblique and transversalis muscles were likewise split in the direction of their fibers, and the juncture of these two incisions was carried across the posterior sheath of the rectus. The rectus muscle was withdrawn and the peritoneum was opened in a transverse direction. The gall-bladder presented a normal aspect, but to its right there projected from the inferior surface of an apparently normal liver a firm nodular tumor the approximate size of a large orange. The gall-bladder was slightly adherent to the left side of the tumor and was dissected from the latter above the line of cleavage, which could be followed backward into the substance of the liver, thus permitting the tumor to be shelled out intact with only moderate loss of blood. Bleeding from the substance of the liver was controlled by electric coagulation, and the raw area of the under surface of the liver was almost completely closed by a transverse suture of plain catgut. The abdomen was closed with chromic catgut in the muscular layers and with silkworm gut in the skin. No drains were inserted. Convalescence was uneventful.

At operation the liver appeared entirely normal, and in particular exhibited absolutely no evidence of cirrhosis or other pathological phenomena related to the possible origin of the tumor. Macroscopically the round tumor presented a roughly nodular external aspect and measured about three inches in diameter.

Microscopic examination of a section of the tumor revealed hepatic parenchyma which was divided into unequal lobules by hyperplastic interstitial fibrosis and bile channels, and advanced interstitial fibrosis in the portal areas, with numerous lymphocytes and an occasional leukocyte which indicated a process that was still active. The bile ducts were hyperplastic and in certain areas approximated neoplastic activity, although the cells were regular and polarization normal.

Diagnosis. Liver tissue exhibiting portal cirrhosis with active hepatitis and hyperplasia of bile ducts.

This picture presented, therefore, an encapsulated tumor mass readily shelled off from the inferior surface of the liver, which on section was found to exhibit all the usual characteristics of liver tissue involved in an active cirrhotic process. At the same time the parent organ appeared grossly normal and the patient free from all clinical evidence of disease. In effect, the mass was a histoid tumor that was the seat of focal cirrhosis, but without signs of malignancy, i.e., a benign hepatoma.

In the face of the above facts the etiology must remain, for the present at least, obscure. It is, of course, not clear whether this mass arose from a congenital cell-rest which later developed inflammatory activity, or whether an area of focal cirrhosis became localized as an extra-hepatic tumor. The well marked encapsulation of the mass and the individual's apparent freedom from symptoms might point to the former origin. On the other hand, descriptions of previously recorded cases would tend to support the latter view. Nevertheless, none of the cases reviewed exhibited this association of apparently normal tissue in the parent organ with an active pathological process in the histoid tumor.

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THE VANISHING LUNG, REPORT OF A CASE OF ADVANCED BULLOUS EMPHYSEMA *

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THE title of this paper is not original Burke,¹ in 1937, first used the term in reporting the case of a white man of 28 with advanced bullous emphysema whom he had followed for five years and who finally died and came to autopsy Serial roentgenograms in this case revealed the progressive increase in size of these bullae until, just before his death, there was little remaining lung substance Burke, in reporting the case, stated that it was one of the most advanced cases of bullous emphysema on record I studied the prints from the roentgenograms of this case and feel that the case I shall report to you in this paper, in so far as roentgenographic evidence of advancement is concerned, is more advanced than his

Pulmonary emphysema may be defined as a condition of the lungs brought about by over-distention of alveolar walls with a resultant loss of their elasticity and finally their rupture

Christie² has subdivided pulmonary emphysema into four types (1) Chronic obstructive or hypertrophic emphysema, (2) senile or atropic emphysema, (3) acute vesicular emphysema, and (4) localized or compensatory emphysema

It is not within the province of this paper to discuss these various forms in detail As a matter of opinion I am not convinced that any of these forms, with the exception of chronic obstructive emphysema, are clinically important Senile emphysema is not so much a condition of the lungs as it is of the chest wall Best and Taylor³ advance the theory that this is a postural emphysema A degeneration of the vertebral discs of the thoracic vertebrae takes place in these old people causing kyphosis of the thoracic spine The anteroposterior diameter of the chest becomes larger, and the lungs enlarge to fill the larger thoracic space There is little reduction in the vital capacity, little change in the oxygen saturation of the blood, and few symptoms in these cases

Acute pulmonary emphysema has been observed in mountain climbers both in the Alps and the Andes, and as the condition has appeared to be temporary, there being no permanent emphysema resulting, it would appear that we may dismiss this form of emphysema as being of little more than academic interest

Compensatory emphysema has been the term applied to hypertrophy of a lung when the contralateral lung or a part of a lung has been thrown out of

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function by a pneumothorax, by thoracoplasty, or by atelectasis. If this is true emphysema at all it is probably not of great clinical importance.

Chronic obstructive emphysema is the type of pulmonary emphysema in which we are interested because this is the clinically important form and the cause of the vanishing lung. It seems wise to discuss the present conception of this treacherous and insidious disease, for its incidence is high, its crippling effects on those it strikes considerable and often most distressing. What then is the etiology of chronic obstructive emphysema? Many theories have been advanced to explain it. For years we have heard that glass blowing and the blowing of wind instruments have been important causes. Laennec was the earliest proponent of this theory which came down through the ages with no more proof to substantiate it than the statement of its originator. Christie⁴ did much to disprove this theory. He made a careful study of the literature and quoted the reports of many investigators who had examined large numbers of players of wind instruments in bands and just as many glass blowers and who had found almost no cases of clinical emphysema among them. In fact, Christie found only one observer who could produce any evidence in favor of the theory that glass blowing and the blowing of wind instruments produced the disease. This was Matussewitsch (1934), a worker in the Leningrad Institute for the Study of Occupational Diseases. Christie found many discrepancies in Matussewitsch's report and was of the opinion that it could not withstand careful analysis.

It appears that there is only one theory that does withstand careful analysis and that is the theory of chronic alveolar strain plus partial bronchial obstruction. It is a conceded fact that the vast majority of patients with pulmonary emphysema have been afflicted with some chronic lung complaint, such as asthma, chronic bronchitis, bronchiectasis, pulmonary tuberculosis, silicosis, or possibly bronchiogenic carcinoma. In other words they have been subject to persistent cough for long periods. Cough alone, however, is apparently not enough. The mechanism responsible appears to be the repeated insults to the alveolar walls brought about by repeated sudden increases of intra-bronchiolar and intra-alveolar pressure during the act of coughing, with the additional important factor of the partial obstruction of these bronchioles owing to the presence of mucus and to scarring from fibrosis and pulmonary arteriolar sclerosis. This obstruction is often of such a nature that, valve-like, air can get through on inspiration but on expiration, as the bronchioles contract, air cannot get out but is trapped within the alveoli distending them. This happens so often and the alveolar walls are in such a state of over-distention that finally the elastic fibers undergo degeneration and the alveolar walls lose their elasticity. After elasticity has been lost further stretching may cause the alveoli to rupture. When this happens several things may occur. If the alveoli so stretched are near the surface of the lung the air liberated when they rupture may separate the pleura from the underlying alveoli, and a blister or emphysematous bleb form on the surface of the lung. Later, due to some sudden exertion or strain on the part of the individual so affected, this bleb may rupture allowing air to get into the pleural cavity, thus causing a spontaneous pneumothorax. If the alveoli so affected are considerably below the surface of the lung they may rupture into other alveoli, and by coalescence a cavity may form within the lung.

with the formation of a bulla. These emphysematous bullae are connected by small openings with the bronchioles for gas samples have been taken from them and upon analysis have shown atmospheric air.

Miller⁵ in 1926 was the first to make the distinction between blebs and bullae. Miller cut open these emphysematous sacs in the lungs of those who had died

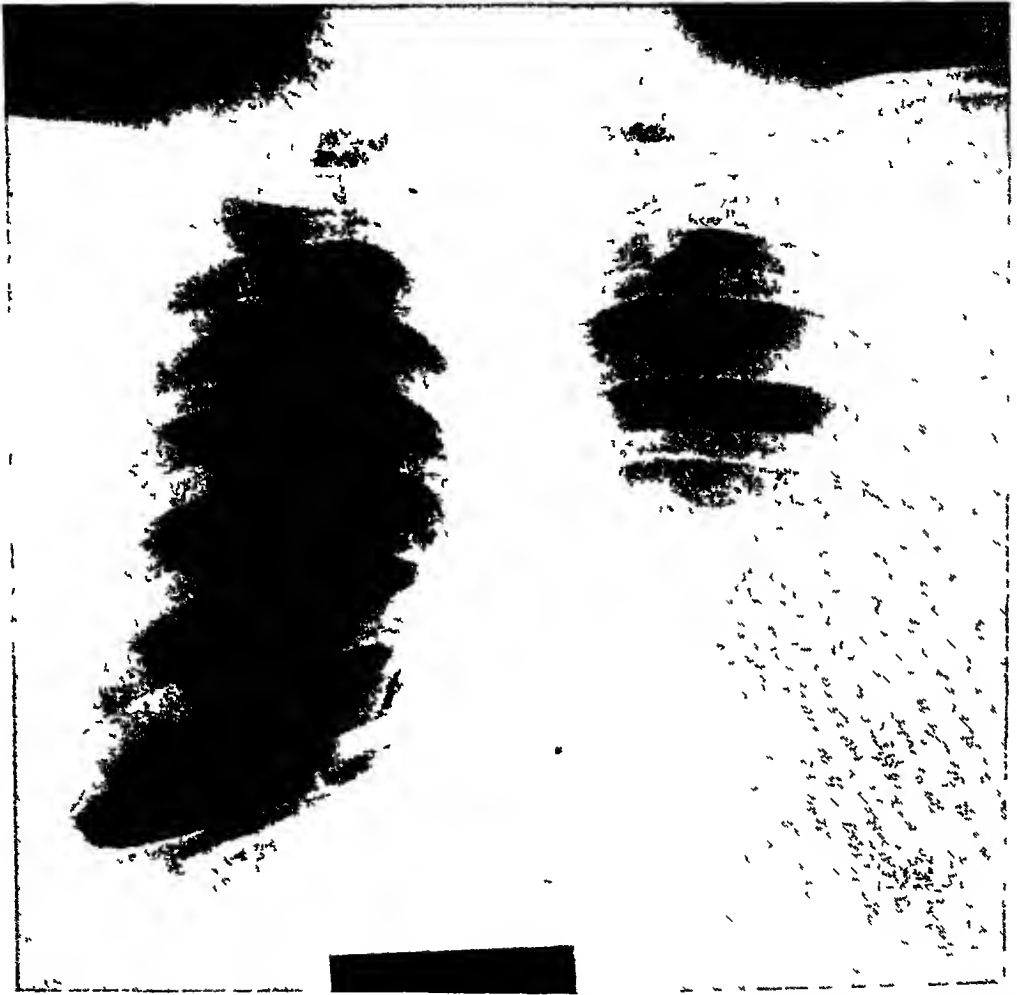


FIG 1 Postero-anterior plate showing complete absence of lung markings in the entire right hemithorax except for a cobweb-like fibrosis at the extreme base. There is absence of markings in the upper half of the left lung field with increased markings in the lower half of this lung. There is no mediastinal shift, no enlargement of the heart, and no evidence of collapsed lung margin.

and studied histological sections of them. He was convinced that the condition of the alveoli surrounding a bulla differed from that of a bleb in that in the case of the bulla the adjacent alveoli were distended, whereas the alveoli beneath a bleb were compressed.

Miller's^{5,6} conception of a bleb is that it is a thin walled bladder-like prominence on the surface of the lung caused by air from ruptured alveoli near the surface of the lung pushing the pleura out and separating it from the underlying alveolar walls. A bulla, on the other hand, is a collection of air formed by

vesicular emphysema and contained within the lung, and though it often projects beyond the surface of the lung it is covered by intact pleura. This distinction may appear to be a rather fine one. Some observers use the terms synonymously. Much remains to be done in the fields of pathology, histology, and physiological chemistry before the true conception of emphysema and its physical manifestations can be confidently stated.

Christie² has pointed out that overstretching and rupture of the lung alveoli are most apt to occur where the lung is least supported, namely at the apex and along the lung margins. He likewise explains the typical barrel-chest conformation of the emphysematous thorax as due to the loss of the elastic pull of the lung when its elasticity disappears, the chest thus assuming permanently the shape it normally assumes only in deep inspiration. This increase in volume of the thorax tends to impair function. The elasticity being lost the lung is unable to deflate by the normal passive process of elastic recoil, and it becomes necessary for the accessory muscles of respiration to squeeze the air out of this failing lung. Expiration becomes prolonged. There is a reduction in total as well as vital capacity, with an increase in residual air.

The chief symptoms of patients with pulmonary emphysema are dyspnea and cough. Kaltreider and Fray⁷ believe the dyspnea can be explained by the mechanical impairment of the respiratory bellows. The sharp rebound of the normal lung occurring at the end of inspiration is an important mechanical factor in the efficient ventilation of the alveoli. It is lost in the emphysematous lung, resulting probably in a slower diffusion and thereby faulty aeration of the blood. The cough, according to Christie,² is due to bronchial irritability and to chronic bronchitis with which these patients are afflicted. The plum-colored cyanosis, so common in emphysematous individuals, may be partly explained by a compensatory polycythemia and partly by a carbon dioxide retention in the blood.

Dyspnea becomes more and more troublesome and finally oxygen must be resorted to periodically. Many patients succumb to pneumonia while others die of heart failure. A few succumb to the accident of spontaneous pneumothorax.

The diagnosis of chronic obstructive emphysema is chiefly roentgenographic. We have been well aware of the presence of emphysema by the brilliant areas of rarification in which no lung markings could be seen. The significance of fine hairline curved and annular shadows in the films adjacent to these areas of rarification, however, has been missed or misinterpreted by many observers in the past. Some have considered them as tuberculous cavities whereas others have believed them to be localized pneumothorax pockets. Miller⁸ in 1933 reported the case of a negro laborer of 66 who had pulmonary tuberculosis and in whose lung a large emphysematous bulla had been mistaken for a tuberculous cavity. Repeated sputum analyses in this case had been negative for tubercle bacilli, and only at autopsy was the real nature of the cavity ascertained. This is not an uncommon mistake. It has probably sent more than one non-tuberculous patient to a sanatorium.

Friedman⁹ considers these annular shadows to be zones of atelectasis in the alveoli adjacent to blebs and bullae caused by compression and to substantiate this quotes the earlier work of Laurell,¹⁰ who, he states, was the first to prove experimentally that blebs and bullae cast ring-shaped shadows on the roentgenogram. Friedman further states that blebs and bullae are occasionally found in the lung in the absence of generalized emphysema.

The gross pathology of chronic obstructive emphysema is interesting. The lung is voluminous and, as Richards¹² brings out, has a pale gray instead of a normal pink surface. In Burke's advanced case when the chest was opened the lungs ballooned out and spilled over the chest cavity as under pressure. Emphysematous lung does not crepitate, but pits on pressure. Histologically there is a pulmonary arteriolar sclerosis and increase in the connective tissue. The



FIG 2 Lateral plate in which no lung markings are apparent except at the extreme base. No evidence of mediastinal tumor is seen.

bullae, seen within the lung substance, usually connect with bronchioles although in some cases even on most careful examination no such openings could be found.

The prognosis of chronic obstructive emphysema is not good. Recovery is out of the question. The process spreads and as bullae increase in size good lung tissue becomes either compressed or over distended until less and less lung remains. In Burke's case practically nothing was left in the left chest cavity but a giant bulla occupying four-fifths of the space. There were only a few fibrous septal strands at the base of the left lung.

In the treatment of these cases it should be emphasized that in advanced cases relief is only temporary. In all cases, early and advanced, the patient with emphysema should be protected as much as possible from acute respiratory infections which would certainly aggravate his chronic condition. Life in a dry warm climate at an altitude below 3000 feet would be the ideal. No excessive muscular strain such as heavy lifting or strenuous exercise should be allowed, not only because this would add to the burden of an already overstrained circulation but also because it might bring about, from sudden rupture of emphysematous tissue, the dangerous accident of spontaneous pneumothorax. The patient should live his life at a slower tempo and develop a philosophy of life which will enable him to do so and still be happy. Unfortunately the economic angle enters the picture here, as it does in most chronic illnesses, and the man with advanced emphysema who must work hard for a living is indeed to be pitied.

CASE REPORT

S P F, a white American male of 41, was first seen by me at his residence on the night of January 24, 1940. He complained of having had a very severe chest cold for two days, with a cough so distressing that the preceding night he had been unable to sleep because of it. There had been no chill, no frank hemoptysis, no blood-tinged or prune-juice colored sputum, in fact very little sputum at all. There was slight chest pain on coughing but not on inspiration. There was considerable dyspnea during and after a coughing spell, and the cyanosis which was slight at rest was intensified and plum-colored during these coughing attacks. The patient stated that for some months, perhaps for a year or more, he had noticed increased breathlessness on exertion and likewise that he was unable to sleep on the left side without coughing and becoming breathless. The significance of this last symptom was not clear at the time, but became so later.

The past history revealed that the patient had had epilepsy from early childhood, with grand and petit mal at infrequent intervals. He had had no attacks for nearly a year and one or two attacks a year had been about his limit. He had had diphtheria and acute nephritis in early childhood and pneumonia twice before he was 10. At the age of 11 he had had acute rheumatic fever following which he had no symptoms referable to his heart, and apparently no one had ever detected any signs of mitral or aortic valvular disease. He had none at the time of examination, at any rate. While at school and college he had played class hockey and other less strenuous sports without any abnormal symptoms appearing. There is only one clue as to the duration of the disease with which he is afflicted. While at college in 1917 a routine physical examination upon admission revealed his chest expansion to be four inches. Two weeks before his recent acute respiratory infection, in early January of 1940, he had gone to a certain New York gymnasium for "conditioning" and when examined there his chest expansion was nil. In spite of this he was permitted to take the strenuous "conditioning" exercises and could not understand why it took him so long to recover from the dyspnea brought on by them. No one else taking the course appeared to be bothered this way. It puzzled him, but he explained it as no doubt being due to the fact that he was "out of condition" and overweight. His weight in college had been 140, his present weight 190.

Upon physical examination the patient appeared slightly cyanotic, dyspneic, and overweight. His height was 5 feet 11 inches, his weight 190 pounds. His pupils reacted well. His teeth were false. He had a history of many abscessed teeth. His heart sounds were somewhat distant but otherwise of good quality. No murmurs could be heard. His chest, a broad heavy one and not a typical "barrel chest,"

was resonant throughout. The breath sounds, except at the left base, were absent, and many sibilant and sonorous râles were heard from about the level of the fourth thoracic spine on the left to the extreme base. No signs were heard on the right. The true significance of these signs was not appreciated at the time. The remainder of the physical examination was negative except for a blood pressure of 180 mm Hg systolic and 80 mm diastolic. The temperature by mouth was normal, the pulse rate 90.

I felt that the patient had an acute bronchitis, but that in view of his general appearance, the rather unusual chest signs, and the elevated blood pressure it would be wise to have him admitted to the hospital for careful study. He was given codeine for the control of his cough during the night and the following morning was admitted to Scrymser House, St. Luke's Hospital.

Laboratory tests of the patient were as follows:

Urine—clear, acid, 1 024, very faint trace of albumin, no sugar. Microscopically no casts, pus, or red blood cells were seen.

Blood Kline test was negative. Blood count: hemoglobin 105 per cent (15.3 grams), red cells 5,000,000, white cells 12,500, polymorphonuclear leukocytes 78 per cent, lymphocytes 18 per cent, monocytes 3 per cent, eosinophiles 1 per cent. There was a slight shift to the left. The red cells were normal in appearance.

Blood urea nitrogen 9.8 mg per 100 cc. Fasting blood sugar 143.0 mg per 100 cc. Blood cholesterol 180 mg per 100 cc. Blood chlorides 5.0 per cent.

The electrocardiogram showed normal sinus rhythm, right axis deviation, auricular and ventricular rate 70, slightly low voltage, PR interval time 0.19 sec, QRS complex 0.08 sec, notched P-waves in all leads, T-waves upright in all leads, Lead IV CF normal.

Stereoscopic roentgenograms of the chest revealed an absence of lung markings in the entire right hemithorax except for a few fibrotic cobweb-like strands at the extreme base. The upper half of the left lung field, corresponding to the left upper lobe, revealed the brilliancy characteristic of the absence of lung tissue, whereas the lower half of the left lung field, corresponding to the left lower lobe, showed increased markings.

Fluoroscopic examination of the chest revealed a normal although somewhat diminished excursion of the diaphragms, the right having an excursion of approximately an inch, the left approximately two inches. Upon inspection in the oblique and lateral views no evidence of tumor mass could be seen in the mediastinum. The heart was not enlarged.

The evidence produced by the roentgenograms came as a complete surprise. This patient had been seen by six or eight physicians in a period of 20 years and no chest roentgen-rays had been taken prior to this, in spite of the fact that in 1936 he had been carefully studied in a large medical center in which gastrointestinal roentgenographic series, blood studies, basal metabolism, and other tests were made.

Looking at the case in retrospect it became clear why dyspnea on exertion was becoming more pronounced as time went by. It also explained the patient's discomfort while lying on the left side at night. By so doing he would splint the only part of the lung which was functioning and having no lung capacity on the right he naturally became cyanotic and dyspneic.

It was impossible to date exactly the beginning of this disease. The fact that the patient's chest expansion at college in 1917 had been four inches suggests that it did not date back to that period. At least, if he did have emphysema at that time it must have been slight.

The etiology of this case is probably that of most cases of emphysema. There are many theories, none of which can be proved. It is true that this patient had numerous respiratory infections, including pneumonia twice, in early childhood. Likewise he had been a very heavy smoker all of his adult life and had had what he

termed a cigarette cough for years. It is quite probable that excessive wear and tear on the alveolar walls caused by cough and partial obstruction of the bronchioles by mucus were the causative factors in this patient's case. The possibility of aspiration during one or more of his grand mal seizures has been considered but discarded as unlikely.

As soon as the roentgenograms of the chest had been seen it seemed obvious that we were dealing with bullous emphysema. The only other possibilities to consider were spontaneous pneumothorax and the "balloon cysts" of congenital cystic disease. If it were the former the patient should have had severe symptoms at the onset of the accident. He did not. Likewise, the lack of mediastinal shift and the bilateral involvement are factors which would rule against spontaneous pneumothorax. Also the border of the collapsed lung should be well defined in cases of spontaneous pneumothorax. As to congenital cystic disease, a rare condition at any age, it is extremely rare at 41, although Wood¹² reported a case in a man of 43. The fact that symptoms in this patient were relatively recent and the fact that he remembered that his chest expansion in college in 1917 was four inches are against the condition's having existed at that time.

The functional power of the remaining lung tissue was studied by Dr. Dickinson, W. Richards, Jr., and Dr. André Courmand. The results of these tests were as follows:

Lung Volumes	Before Vaponephrin	After Vaponephrin
Vital capacity in liters	2.378	2.572
Residual air in liters	3.447	
$\frac{\text{Residual air} \times 100}{\text{Total lung volume}}$	59.2%	
Maximum breathing capacity in liter/minutes	32.2	47.2

Rate of Oxygen Removal per Liter of Ventilation in c.c.

At Rest	During Exercise
41.0 (normal—47 c.c.)	45.8 (normal increase 6-7 c.c.)

Arterial Blood Oxygen Hemoglobin Saturation

At Rest	After Exercise
94.2	94.5

Status of Circulation during Infusion Test

	At Start	At End
Venous pressure (mm H ₂ O)	85	120
Circulation time sec	14	
Vital capacity in liters	2.205	2.230

These studies revealed a remarkable functioning power of the remaining lung tissue, more than we had hoped for.

Treatment presents a difficult problem. Croswell and King (1933)¹³ reported the case of a boy of two and a half years who had a large "balloon cyst" in his lung, into which they had injected, through the chest wall, iodized poppy seed oil. They believed that a bronchus opened into the cyst and that if they could obliterate this opening the air in the cyst would absorb and the atelectatic lung reexpand. They turned the child over in various positions so that the oil would come in contact with all of the cyst wall. A serous exudate formed, the opening evidently was sealed off, and the lung reexpanded as they had hoped. This patient was well at the end of two years' observation. Wood¹⁴ criticized this procedure, stating that it was not

without risk to the patient. It seemed to Dr James Alexander Miller, with whom I consulted in the case, and to me that such a procedure with our patient would be dangerous and unwise. The fact that the affair was bilateral increased the risk, and we felt that inserting a needle through the chest wall into the bullous cavity might bring about sudden spontaneous pneumothorax with the death of the patient.

In view of the results of the functional lung studies it seemed possible that the patient with proper care might live for several years, even perhaps many years, in reasonable comfort. It was decided that he should move to Tucson, Arizona, for the winter and spring months to insure clear, dry air, with the hope that this might lessen the likelihood of respiratory infections. He was instructed to avoid strenuous exercise and heavy lifting, and was cautioned about smoking and the use of alcohol, as the former would act as an additional bronchial irritant and the latter would elevate his pulse rate and add to the load of an already overburdened circulation as well as lower his resistance. This man has been a very heavy smoker for 20 years or more which may be a factor in causing this condition. A diet which was sufficient to maintain good health but which would not increase his weight was prescribed. As the patient was overweight it was felt that it was wise for him to reduce considerably. The diet was low in fats and carbohydrates but high in protein, vegetables, fruits and vitamins. He was advised to use an abdominal belt which increases intraabdominal pressure and thus elevates the diaphragm and increases the vital capacity. Alexander and Kountz¹⁴ devised such a belt in 1934 and in 25 cases found that it increased vital capacity 39 per cent. As the patient is in a position to carry out these directions, such hopes for his future seem within the realm of probable achievement.

SUMMARY AND CONCLUSIONS

1 Chronic obstructive emphysema is an insidious disease of the lungs in which the elasticity of the alveolar walls is lost, with the result that these walls rupture.

2 When the air from the ruptured alveoli is contained within the lung itself and covered by intact pleura the resulting cavity is known as a bulla and this type emphysema is bullous emphysema.

3 The probable cause of emphysema is not glass-blowing or the blowing of wind instruments but, it seems reasonable to assume, the wear and tear on alveolar walls due to sudden and frequent increases in intraalveolar pressure during the act of coughing in patients afflicted with asthma, chronic bronchitis or some other pulmonary disease of chronic character. The added factors of mucous obstruction in the bronchioles, and fibrous scarring and arteriolar sclerosis are likewise of considerable importance in the etiology.

4 A case of far advanced bullous emphysema with good functioning power of the remaining lung tissue is reported.

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A CASE OF PANCREATIC LITHIASIS

By D B FAUST, M D, F A C P, and W G BRANDSTADT, M D,
Washington, D C

ALTHOUGH some 113 or more cases of pancreatic lithiasis have been reported, it is still rarely diagnosed during life. In 1937 Hochstetter¹ was able to find only four cases diagnosed by roentgen-ray before operation and 30 diagnosed on the operating table. The rest of the reported cases have been revealed only at autopsy. Since the symptoms produced are variable and quite unreliable, and since the stones found in the pancreas are ray-opaque, the roentgen-ray is our most valuable means of diagnosis in this condition. As was pointed out by one of us (D B F) in 1935,² it is necessary to rule out other abnormal opacities found in the abdomen. A cholecystogram will aid in ruling out gall-stones and a pyelogram in ruling out kidney stones. As a further aid in ruling out these conditions and calcified retroperitoneal or mesenteric lymph nodes, fluoroscopy and films taken in the lateral and oblique positions should be used. Pancreatic disease is to be suspected if in the gastrointestinal series there is a deformity and elongation of the duodenal arc.

CASE REPORT

W D, a colored male, 45 years old, a huckster by occupation, gave a history of repeated hospitalization for "stomach trouble" since 1918. The records of this hospital † revealed seven previous admissions in which abdominal distress and a chronic cough were the chief complaints. The chest trouble was described as a chronic, productive cough with occasional pains in various parts of the chest. The gastrointestinal symptoms consisted of constant, dull, epigastric pain with periodic attacks of rather

* Received for publication November 14, 1939

† Walter Reed General Hospital, Washington, D C



FIG 2

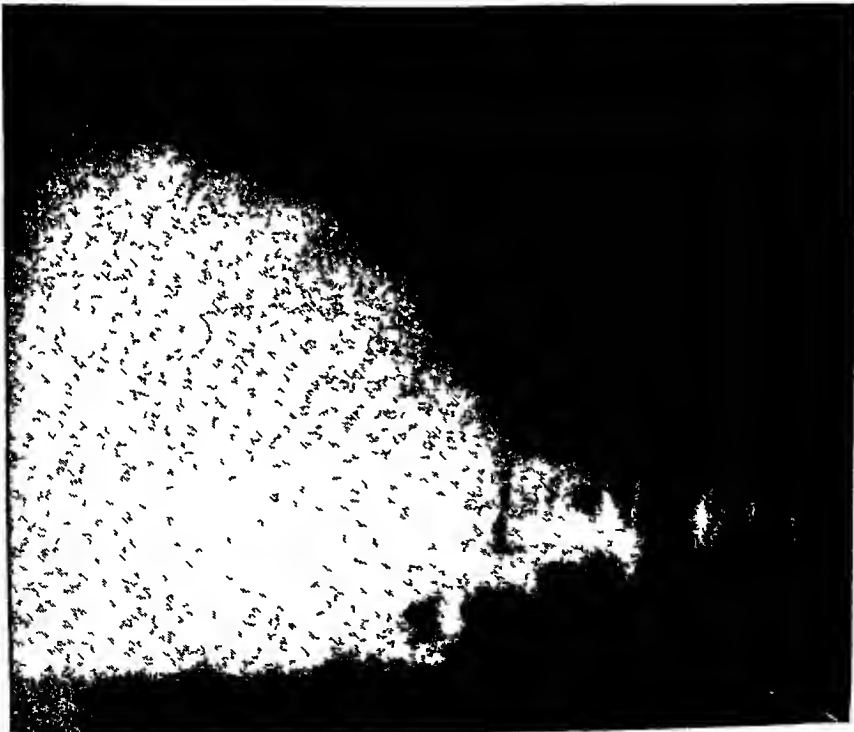


FIG 1

severe epigastric pain, constipation, intolerance to coarse foods, loss of about 30 pounds in weight, weakness and occasional vomiting. He maintained that the symptoms had persisted, unchanged as to severity, since 1918. About one year previously he had noted a moderate jaundice which lasted for about eight months, but during this time there was no change in the character or severity of his other symptoms. At the time of his last admission, approximately six years previously, he had complained of a dull aching and dragging pain in the epigastrium, radiating to the hypochondrium bilaterally, not related to ingestion of food.

Physical examination revealed a poorly nourished male weighing 112 pounds, with a few inconstant coarse râles in both lungs, moderate enlargement of the liver, moderate tenderness over the gall-bladder on deep palpation, associated with some muscular resistance in this region. Many teeth were missing and there was a moderate kyphosis.

Tentative diagnoses of chronic bronchitis, chronic gastritis and cirrhosis of the liver were made.

Before completion of the studies it was noted that while in the hospital he was subject to irregular attacks of acute epigastric pain not related to food or to evacuation of the bowel, and not relieved by alkaline powders or by enemata. Between attacks he was quite cheerful, but during the attacks his facial expression was one of intense pain. At times he would bend sharply forward grasping the epigastrium with both hands, and at other times he would lean over the bed and groan. Muscle guard was a constant finding in the upper abdomen, but during the attacks there was true rigidity.

The survey revealed moderate cloudiness of both maxillary sinuses, a poorly functioning gall-bladder, a bizarre but rather constant deformity of the duodenal bulb and a normal barium enema. It was on the films of the gastrointestinal series that a solitary calcified nodule in the liver, as well as fine and medium-sized calcified areas in the region of the pancreas, were first noted. Later films of the abdomen including lateral and oblique views fixed the position of the multiple, small calcified areas as being in the pancreas. Urine, feces, sputum and blood examinations were all essentially normal. Blood Wassermann and Kahn, gastric fractional analysis, blood sugar, bromsulphalein, glucose tolerance, electrocardiogram, roentgen-ray of the chest and proctoscopic examination were all within the normal range. The icterus index was 10.

Careful observation on the ward later disclosed that the attacks of epigastric pain were definitely related to meals in that even the smell or the sight of food would induce the pain. It was further noted that if he ate rapidly he could sometimes eat most of his tray before the onset of acute pain. Because of the associated gall-bladder disease and the severity of the attacks, surgery was advised, but it was refused and the patient was discharged from the hospital unimproved, with a diagnosis of pancreatic lithiasis based on clinical and roentgen-ray findings.

About 18 months later he had an attack of agonizing pain which caused him to writhe on the floor and he was re-admitted to this hospital. Examination revealed extreme tenderness associated with moderate rigidity and rebound tenderness in the midepigastrium. He readily consented to operation. On exploration gall-bladder adhesions were released. The gall-bladder was otherwise normal. The pancreas was enlarged to about five times the normal size, indurated, and so distended that the usual lobulated appearance was obliterated. The surgeon was unable safely to expose the head of the pancreas except posterior to the first portion of the duodenum. At this point the pancreas was incised and one small, very white calculus removed. Many calculi in the terminal ducts could not be removed. Biopsy showed no malignancy. The convalescence was smooth. The patient's appetite improved and he gained over 20 pounds in six weeks. About 10 weeks after operation there was a sudden return



FIG 4

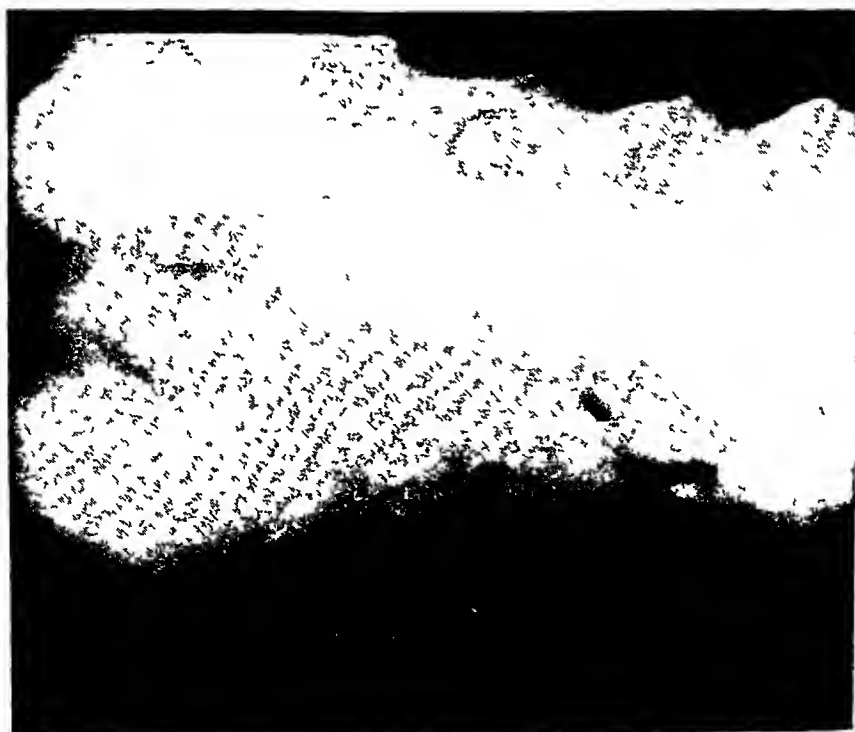


FIG 3

of his pain which we attributed to a blocking of the main pancreatic duct with another stone. We do not believe that when the stones are distributed as they are in this case there is any hope for permanent cure, but will recommend another trial at surgery.

This case presented no exception in the elusiveness and inconstancy of the symptoms and findings during prolonged and repeated examinations. The most common and constant symptom in this case was epigastric pain, not related to meals at first but later caused by the sight or smell of food.

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EDITORIAL

THE FEMALE HORMONES

BECAUSE there is still much misapprehension as to the conditions in which these hormones are effective and as to their limitations, a brief authoritative discussion of the available pertinent facts concerning them seems desirable. The following summary has been prepared by Dr. Elmer L. Sevringhaus^{*} and is published as an editorial in order to help toward a clearer understanding and more intelligent use of these preparations.

The hormones which are distinctively female are the estrogens and progesterone. The first group includes estradiol (the most potent), estrone (next in potency but more commonly known and used), and estriol (still less potent). There are also a large number of similar compounds which are of biological significance in limited situations but of little importance to the clinician. The synthetic estrogen, stilbestrol, must be kept in mind from a therapeutic point of view. Progesterone, product of the corpus luteum, is unique and there are no similar naturally occurring compounds of significance.

Physically these compounds are all solid, waxy materials, called steroids, which are very poorly soluble in water but more soluble in alcohol and oils. The water solubility of estrone is 2 mg. per liter, or 20 international units per c.c., which is somewhat greater than the highest concentrations of the hormone found in any tissues or body fluids. For therapeutic purposes the greater solubility in oils, above 10,000 international units per c.c., is of real importance. Perhaps this solubility in oils has something to do with the distortions of reproductive function which occur in obesity and which are often relieved by weight reduction alone.

Chemically these hormones are closely related, as derivatives of a rather complicated polycyclic compound, pregnane. The same statement applies to the male hormone, testosterone, to the hormone molecules derived from the adrenal cortex, and to a number of other biologically active substances, some in the field of food materials, others of drugs. The chemical tests for identification of any one of these compounds are involved, and the color reactions are usually not specific enough for identification of any one as distinct from another. The assay by means of biological reactions is similarly specific only in the sense of identifying a compound which is purified from the others of similar activity so that its activity per mg. can be determined. In

^{*} Summary of a lecture delivered before the American College of Physicians, April 22, 1942, at St. Paul, Minnesota.

For further details regarding these hormones, readers are referred to (1) ALLEN, E., DANFORTH, C. H., and DOISY, E. A. Sex and internal secretions, second edition, 1939, Williams and Wilkins, Baltimore, and (2) Glandular physiology and therapy, second edition, 1942, American Medical Association, Chicago.

the body estradiol is most active, it is easily changed to estrone, probably in the liver, and then to estriol. Only these latter two compounds occur in significant amounts in the urine, and then only somewhat less than 10 per cent of the original material is so found. The fate of the rest of the estradiol is still unknown. Progesterone is converted in the body to pregnandiol, which is then conjugated largely with glycuronic acid, for urinary excretion. Even this process carries for only an uncertain although large fraction of the progesterone. Other metabolic products of progesterone have not been identified.

The sources of all these ovarian hormones include the ovaries, and during pregnancy the chorionic tissues as well. Estrogens appear to come from all parts of the ovaries, the progesterone probably from the transformed luteal cells only. The quantitative aspects of this secretion are known in only the roughest way, owing to the lability of the compounds, the lack of knowledge of all end products, and the unmet need for specific methods for determining any one of the estrogens in the presence of the others.

Estrogens as a group are stimulants of tissue growth, with effects most marked in the myometrium, endometrium, vaginal epithelium, and mammary ducts. The other activities include stimulation of rhythmic contractions in the uterus and Fallopian tubes, relaxation of the muscles in blood vessels, the stimulation of the secondary sex characters, and a reflex activity upon the anterior pituitary. This latter effect is a composite of stimulation of the pituitary by brief application of moderate amounts, and inhibition of pituitary function by sustained exposure to large amounts of estrogen. The variations in the amounts of pituitary and estrogenic hormones are thought to be fundamental factors in the control of rhythmic action of the ovaries. The quantitative laws cannot yet be formulated.

Progesterone induces relaxation of myometrial contractions, reduces the sensitivity of the uterus to posterior pituitary hormone, interrupts the effect of sustained estrogenic secretion on the uterus, but most important of all progesterone induces the transformation of endometrial glands from the type known as proliferative to that called progestational (secretory for mucin, glycogen, and possibly fat). Progesterone is also the stimulant to development of mammary acini preparatory to lactation.

Diagnostic procedures are directed to identify the presence of these two types of hormone, and to determine the amounts active. Histories of patients will show the presence of estrogens, but nothing short of pregnancy will prove progesterone. Tissues obtained by biopsy or curette from the endometrium will show estrogens or progesterone, and will give a roughly quantitative measure of the activity. Microscopic study of vaginal cells, obtained by smear technic, furnishes a better quantitative gauge of estrogens, but so far it tells nothing about progesterone. Urinary examination for pregnandiol is a chemical check on progesterone with quantitative significance of fair reliability. The use of assays of blood and urine for these

hormones, by either biological or color tests, is still a fascinating problem for use in investigative clinics alone

Therapeutic uses of estrogen include (1) stimulation of development in cases with infantilism, amenorrhea, or hypoplasia of the genitalia or breasts. This use is questionable, for it is prone to leave the ovaries less active than before, certainly not more active and able to carry on reproductive function. (2) Relief from dysmenorrhea may occur at times when the cause is a hypoplastic uterus. Such use is not frequently successful. (3) Treatment of sterility by estrogens is empirical, has little evidence to support it, and there may be risks. (4) Rapid maturing of the juvenile or infantile vaginal mucosa induced by estrogens leads to cure of gonorrheal vaginitis when this occurs before puberty. A similar physiological process is utilized in obtaining relief from the distress of senile vaginitis. (5) The chief benefit obtained from estrogenic therapy is relief from the autonomic and psychic symptoms of the climacteric. It is to be prescribed in doses adequate to achieve the relief, without regard to the inhibitory action on the anterior pituitary. Upper limits on dosage are indicated by restoration of bleeding, or uncomfortable stimulation of the breasts or of libido.

Progesterone therapy is helpful in repeated abortion, perhaps also early in threatened abortion. Dosage is still uncertain, but should be 1 mg or more frequently repeated. Menorrhagia may be interrupted at times by use of progesterone in large doses. At times certain types of amenorrhea may respond to progesterone if the amenorrhea is dependent on a rather steady secretion of estrogens. Use of progesterone in the treatment of painful breast swelling is still being tried out.

The following methods of administering these hormones are available. (1) Oily solutions may be given intramuscularly, employing estrone, estradiol as the propionate, the relatively crude estrogenic substance, stilbestrol and its derivatives, and progesterone. (2) Probably all these might be given by vaginal suppositories, but this is done now only with estrogens in treating vaginitis. (3) Inunction of any of these compounds in oils, ointments, or in alcoholic solution is feasible, and is of real interest in estrogens for climacteric control. (4) Implantation of pellets under the skin for prolonged absorption is interesting, but probably not of permanent importance, since oral use is so easy. (5) Orally estradiol is not an economical form of therapy, but estrone or estrogenic substances may be used in this way profitably. Doses should be divided into one or more portions daily for most efficient use. Stilbestrol owes its great advantage to its low rate of destruction when given orally. The preparation pregnenolone, a synthetic substitute for progesterone, has some possible future as an orally active substance which produces progestational effects. It cannot be evaluated yet.

ELMER L. SEVRINGHAUS

REVIEWS

Time and the Physician By LEWELLYS F BARKER, M D 350 pages, 23.5 × 15.5 cm G P Putnam's Sons, New York 1942 Price, \$3.50

This is the engaging life story of the much honored and travelled physician, Dr Lewellys F Barker. Aside from being of value in giving us a picture of the eminent physician himself, the book adds to chronicles of the Medical School and hospital of the Johns Hopkins University. Much of the author's personal philosophy flavors the book throughout. Dr Barker has been a pioneer in giving proper emphasis to the importance of studying functional nervous disorders in conjunction with the practice of internal medicine.

Physicians as a group, and more particularly those physicians who are or have been associated with the Johns Hopkins Hospital, will find the book an absorbing account of Dr Barker's own life, as well as an intimate record of the early days of the hospital.

J E S

The Fundamentals of Nutrition By ESTELLE E HAWLEY, Ph D, and ESTHER E MAURER-MAST, M D 477 pages, 25.5 × 16.5 cm Charles C Thomas, Springfield, Illinois 1940 Price, \$5.00

This book should be extremely valuable to physicians and dietitians. It is a clear, concise discussion of nutrition supplemented by convenient, practical tables, charts, ample reference lists and bibliographies.

Section I is a clear explanation of metabolism and modern methods of measuring it. There are tables for calculating surface area and basic metabolic rate, and determining the probability of normality.

Section II deals with the fundamentals of nutrition, discussing briefly but adequately the importance of the various foodstuffs, the method of calculating the energy requirement, the normal diet and some very practical suggestions for planning low cost meals. A long list of references is included at the end of this section, should the reader wish further to investigate the subjects. A similar list of references follows each section.

Section III contains a number of articles on diet therapy written by different physicians. They cover practically every condition in which diet is used as a therapeutic measure, and each article is followed by a summary of the general principles of the dietary treatment.

Section IV on diet planning contains a well constructed table of 100 calorie portions which gives the weight, the grams and calories of protein, fat and carbohydrate, the vitamin content in International Units for all except C which is given in milligrams, and G (B₂) given in S-B Units, the mineral content in grams for eight minerals, the acid or base excess in terms of c.c. normal solution, and uric acid. There are explicit directions for using this table. There is a chapter on the calculation of diets and a table showing equivalents for interchanges in special diets. A table on the potassium content of foods is included in which the foods are divided into 12 groups according to their potassium content. A table on the cholesterol content of foods contains seven groups which should aid in planning diets for gall-bladder disease. There is an excellent summary of adjustments of the normal diet to meet specific therapeutic needs. This table should make the planning of special diets easier for physician, nurse or dietitian. A table on the approximate quantity yield from one pound of common foods should be useful to the person who helps a patient plan a budget diet.

Section V is an appendix which is extremely valuable for the collection of information on food which it contains. There are directions for evaluating the nutri-

tional status of a patient, including an outline for the nutritional history and definite laboratory methods of studying vitamins with lists of equipment needed. A part of the appendix devoted to milk gives the composition of milks of various mammals and standards for grading milk. A discussion of vitamin products includes a summary of costs, potency and dosage which should be extremely valuable to the physician. The appendix includes a number of recipes and food suggestions for special conditions—recipes for the use of glandular meats, for foods without wheat, milk or eggs. There are some special diet instruction sheets and a list of biologic food groups.

This volume is well indexed and should be an excellent aid to the physician who wants a ready reference on nutrition. It is not a large volume, but the information is extremely well chosen and arranged for use.

F J

Surgery of the Ambulatory Patient By L. KRAEER FERGUSON, A B, M D, F A C S, Section on Fractures by LOUIS KAPLAN, A B, M D, F A C S. 923 pages, 16 X 23.5 cm. J. B. Lippincott Co., Philadelphia. 1942. Price, \$10.00.

Surgery of the Ambulatory Patient succeeds, in large measure, in placing at the disposal of the medical profession a book that gives useful information regarding the ambulatory patient, whether the reader be a general practitioner, a beginner in surgery, or an advanced student in the surgical field. In addition, the undergraduate student in medicine may find many informative chapters between its covers such as those on bandaging, dressings, inflammation, chemotherapy, lymphangitis, etc. The practitioner in other fields may gain valuable information on many subjects such as the eye, ear, hemorrhage from tooth extraction, torticollis, bursitis, painful joints, painful backs and a host of other conditions that cannot easily be picked up in any other single textbook. Many subjects are discussed, however, that, in my opinion, should not be interpreted as ambulatory conditions, and the definitive treatment in numerous cases illustrated should be instituted only while the patient remains for a few days in a general hospital.

T B A

COLLEGE NEWS NOTES

As of July 1, 1942, the following physicians who are Fellows or Associates of the American College of Physicians are on active duty in the armed forces of their country

Gordon A. Abbott
W. Osler Abbott
Conrad Acton
Walter P. Adams
Carl R. Ahroon, Jr.
George A. Alden
Edward L. Alexander
Ralph I. Alford
William H. Allen
Stanton T. Allison
James B. Anderson
John B. Anderson
Otis L. Anderson
Walter M. Anderson
Cecil L. Andrews
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Harry G. Armstrong
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Crawford N. Baganz
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John T. Bennett
Thomas W. Bennett
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J. Edward Berk
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Reuben Berman
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Edward G. Billings
Charles T. Bingham
Benjamin J. Birk

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Staige D. Blackford
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Joe P. Bowdoin
Albert G. Bowei
Douglas Boyd
Aubrey L. Bradford
Alonzo F. Brand
Wayne G. Brandstadt
Kenneth A. Brewer
Leon Bromberg
Daniel N. Brown
Ernest W. Brown
Omar J. Brown
Samuel McP. Browne
James G. Bruce
Clyde W. Brunson
Bert M. Bullington
Benjamin Burbank
George G. Burkley
Thomas W. Burnett
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Lee D. Cady
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George R. Callender
George W. Calver
Richard B. Capps
A. Albert Carabelli
Arturo Carbonell
Earl C. Carr
Hubert H. Carroll
Leon D. Carson
Martin G. Carter
Elmer T. Ceder
Frederick Ceres
Francis H. Chafee
Donald T. Chamberlin
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 Herman M. Chesluk
 Edward P. Childs
 Roger M. Choisser
 George D. Chunn
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 Samuel Cohen
 Sander Cohen
 Raphael J. Condry
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 William E. Costolow
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 Wesley C. Cox
 Harold O. Cozby
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 Paul M. Crawford
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 Murray DeArmond
 Elbert DeCoursey
 John S. Denholm
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 Harold A. Des Brisay
 John Dibble
 Paul F. Dickens
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 Henry L. Dollard

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 Henry C. Dooling
 Thomas O. Dorrance
 Alexander S. Dowling
 George B. Dowling
 Charles McC. Downs
 Eugene H. Drake
 Morris L. Drazin
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 Glenn E. Drewyer
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 Stuart O. Foster
 William B. Foster
 Frederick H. Foucar
 Everett C. Fox
 Leon A. Fox

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Arden Freer
Sanford W French
Chester S. Fresh
Victor K Funk
William H Funk

Arthur R Games
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Leon L Gaidner
Stuart N Gardner
Rolland R Gasser
Lawrence E Geeslin
Ernest R Gentry
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William S George
Mark Gerstle, Jr
William T Gibb
*James O Gillespie
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Harold I Ginsberg
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A Allen Goldbloom
Frederick Goldman
Harold H Golz
Benjamin E Goodrich
Burgess L Gordon
Eddie M Gordon, Jr
Harold Gordon
William H Gordon
M Leonard Gottlieb
Kenneth G Gould
G Philip Grabfield
William D Graham
Ben E Grant
Brooks C Grant
Ghent Graves
John A C Gray
Percival A Gray, Jr.
Frederick C Greaves
Eugene W Green
Mack M Green
Mervin E Green
Edward B Grossman
John B Grow

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James W Hall, Jr
William M Hall
William W Hall

William R Hallaran
Harley J Hallett
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Maurice Hardgrove
John Harper
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Forrest M Harrison
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Paul Hayes
James F Hays
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Vincent Hernandez
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Charles C Hillman
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Bartholomew W Hogan
Rufus L Holt
Ralph H Homan
F Redding Hood
Ralph C Hoyt
Edward G Huber
John D Hughes
Edgar E Hume
W Byrd Hunter

Ebner H Inmon
Merritte W Ireland
Cullen W Irish

Waddie P Jackson
Irving W Jacobs
Walter S Jensen
Henry J John
Augustus B Jones
Robert H Jordan

* Missing in action

Allen I Josey
Benjamin Juliar

Warren F Kahle
Paul E Keller
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LeMoyne C Kelly
Paul S Kemp
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Richard A Kern
Baldwin L Keyes
Hugh E Kiene
Floyd V. Kilgore
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S Edward King
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William W Kirk
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Howard F Lawrence
Dwight Lawson
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William H Leake
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B Oliver Lewis
Seaborn J Lewis
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Howard A Lindberg
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Philip H Livingston
Putnam C Lloyd
Victor W Logan
Robert B Logue
Don Longfellow
George Lorenz, Jr
C Ray Lounsberry
John W P Love
Julian Love
Adolph B Loveman
Charles F Lowry
Robert H Lowry
Harold C Lueth
George F Lull
Harold D Lyman

Roger D Mackey
Alexander R MacLean
Robert K Maddock
Patrick S Madigan
James C Magee
Hertel P Makel
William R Manlove
Alexander Marble
David M Marcley
Shelley U Marietta
Albert G Markel
John I Marker
Dean W Marquis
Norval M Marr
Leslie B Marshall
Walter B Martin
Horace P Marvin
Neely C Mashburn
Arthur M Master
F A L Mathewson
Milton J Matzner
John R S Mays
John M McCants
Donald McCarthy
James L McCartney
William U McClenahan
George W McCoy
Frederick L McDaniel
Shaw McDaniel
William O McDonald
Ernest G McEwen
A Park McGinty
Ross T McIntire
Alva B McKie
Edward P McLarney
Christopher J McLoughlin
H Easton McMahon
Delbert H McNamara

John P McVay
 Douglas H Mebane
 John W Meehan
 William B Meistei
 Kent C Melhorn
 Joseph A Mendelson
 Murlin P Merryman
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 Francis R Meyers
 H Clay Michie
 William S Middleton
 Raymond E Miller
 Tate Miller
 Nathan T Milliken
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 A Mogabgab
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 Carlyle Morris
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 Charles S Mudgett
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 William P Mull
 William C Munly
 F F Murdoch
 Willis A Murphy

Walter L Nalls
 Kenneth R Nelson
 Lloyd R Newhouser
 William J Norfleet
 Irwin L V Norman
 Edgar W Norris
 Jack C Norris
 Edward A Noyes
 Robert B Nye

Harry C Oard
 Cleve C Odom
 Harry D Offutt
 Adolph T Ogaard
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 Arthur I. Osterman
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 Victor L Pellicano
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 Frank L Price
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 Richard Z Query, Jr
 Herbert L Quickel
 James W Quinlan

Robert B Radl
 Harold E Ragle
 William O Ramey
 Hilton S Read
 Robert A Reading
 Edward U Reed
 Eugen G Reinartz
 Anthony E Reymont
 Charles R Reynolds
 William F Rice
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 Lyle J Roberts
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 Frederick C Smith
 Hugh P Smith
 Jerome F Smith
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 O Norris Smith
 William L Smith
 Robert F Solley
 James W Sours
 Robert H Southcombe
 Thomas N Spessard
 Aaron A Sprong
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 Gurney Taylor
 James S Taylor
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 Griffith E Thomas
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J Russell Twiss

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J Franklin Waddill
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Additions to this list will be published periodically

NEW LIFE MEMBER OF THE COLLEGE

Dr Clayton B Ethridge, F A C P, Washington, D C, became a Life Member of the American College of Physicians on June 2, 1942

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members.

Walter H Baer, F A C P, Captain, (MC), U. S Army—1 reprint,
Dr Jason Engels Farber (Associate), Buffalo, N Y—4 reprints;
Dr T Lyle Hazlett, F A C P, Pittsburgh, Pa—3 reprints,
Dr Archibald L Hoyne, F A C P, Chicago, Ill—14 reprints,
Dr Vincent W Koch, F A C P, Janesville, Wis—1 reprint,
Dr Paul J Lewis, F A C P, Yakima, Wash—1 reprint,
Dr Walter B Martin, F A C P, Norfolk, Va—4 reprints,
Dr Oscar O Miller, F A C P, Louisville, Ky—1 reprint,
Dr Louis Bonner Owens, F A C P, Cincinnati, Ohio—1 reprint,
Dr Robert C Page, F A C P, Mount Vernon, N Y—3 reprints,
Dr C Graham Reid (Associate), Charlotte, N C—8 reprints,

Dr Abraham Rudy, F A C P , Boston, Mass—17 reprints,
 Dr Leon Schiff, F A C P , Cincinnati, Ohio—1 reprint,
 Dr Samuel Weiss, F A C P , New York, N Y—3 reprints

DR CHARLES F TENNEY ELECTED REGENT

Dr Charles F Tenney, F A C P , New York City, has been elected a member of the Board of Regents of the College to fill the vacancy caused by the elevation of Dr Ernest E Irons to the office of President-Elect Dr Tenney will serve until the next regular election

Dr Tenney has served several years as the College Governor for Eastern New York, a district in which the duties of the Governor are probably heavier than anywhere in the nation His successor as Governor for Eastern New York will be named in the near future •

REGIONAL MEETING OF NEBRASKA MEMBERS

An informal Regional Meeting of Nebraska members of the College was held June 3, 1942, at the Omaha Club, Omaha, Nebr, under the Chairmanship of Dr Warren Thompson, Governor for Nebraska While the meeting was partially of a social character, it was utilized as a discussion meeting of problems affecting the College, with special reports from members who have taken A C P postgraduate courses during the past year and those who were in attendance at the Annual Session of the College in St Paul

Although a large part of the attendance at this meeting came from the local membership, all outstate members were invited, and a fairly good number attended Every member who was present at the St Paul Session took part in the local informal program of discussion on clinics, panels, interesting papers and on postgraduate courses

REGIONAL MEETING OF THE COLLEGE MEMBERS IN MISSISSIPPI

During the meeting of the Mississippi State Medical Association Fellows and Associates of the American College of Physicians in Mississippi held their first regional meeting at a luncheon at the Robert E Lee Hotel, Jackson, May 13, 1942, under the Governorship of Dr John G Archer, F A C P , Greenville

The guest speakers at this meeting were Dr Fredrick A Willius, F A C P , Rochester, Minn, and Dr Ralph Bowen, F A C P , Houston, Tex Dr Willius spoke on "The Frequent Abuses of the Electrocardiograph" and Dr Bowen spoke on "Allergy" Dr Douglas D Baugh, F A C P , Columbus, Miss, was in charge of the program and led a round table discussion

Of the nineteen College members in the State of Mississippi, twelve were present at this luncheon meeting It was decided that the Mississippi members of the College would hold a regional meeting each year during the meeting of their state medical association

AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION HOLDS FORTY-FIFTH ANNUAL MEETING

Under the Presidency of Dr Russell S Boles, F A C P , Philadelphia, the American Gastro-Enterological Association held its forty-fifth annual meeting at Atlantic City, June 8-9, 1942 One of the highlights of the session was the presentation of the Friedenwald Medal to Dr Max Einhorn, F A C P , of New York City, the presentation being made by Dr William Gerry Morgan, M A C P , of Washington

This Association has a total of 188 members, of all classes, of which 112 are Fellows and 8 are Associates of the American College of Physicians. Of its Officers during the past year, all but one are Fellows of the College, including Dr Sara M Jordan, Boston, 1st Vice President, Dr A H Aaron, Buffalo, 2nd Vice President, Dr John G Mateer, Detroit, Treasurer; Dr Julian M Ruffin, Durham, Recorder, Dr J A Bargaen, Rochester, Minn, Secretary, Dr Ernest H Gaither, Baltimore, and Dr A C Ivy, Chicago, Members of the Council, Dr Walter L Palmer, Chicago, Dr Henry L Bockus, Philadelphia, and Dr John M Blackford, Seattle, Committee on Admissions. Thirty-one places on the Atlantic City program were filled by Fellows or Associates of the College

Under the Presidency of Dr W Paul Holbrook, F A C P, Tucson, the Arizona State Medical Association held its annual meeting in Prescott, May 25-30, 1942. Among the guest speakers were

Dr Walter Bauer, F A C P, Boston, Mass—"Arthritis",
 Dr Noble Wiley Jones, F A C P, Portland, Ore—"Arteriosclerosis"

Dr Jay M Garner (Associate), Winnetka, Ill, spoke on "Interesting Proctoscopic Observations in Color" at a meeting of the Institute of Medicine of Chicago, May 22, 1942. Dr Andrew C Ivy, F A C P, Chicago, Ill, presided

Dr Lee R Woodward, F A C P, Mason City, has been chosen President-Elect of the Iowa State Medical Society

Dr Thomas Addis, F A C P, San Francisco, Calif, recently gave a Mayo Foundation Lecture in Rochester, Minn, on "The Treatment of Glomerulonephritis"

Dr William Halsey Barker (Associate), Baltimore, Md, spoke on "The Sulfonamides" at a recent meeting of the South Carolina Medical Association at Columbia

Among the speakers at the annual session of the American Academy of Tuberculosis Physicians held in Atlantic City, N J, June 8-9, 1942, were

Dr Leo L Hardt, F A C P, Chicago, Ill—"Gastroscopic Findings in Far Advanced Pulmonary Tuberculosis",

Carl W Tempel (Associate), Major (MC), U S Army—"Pneumoperitoneum Its Place in Collapse Therapy"

Dr Lowell S Selmg, F A C P, Detroit, Mich, spoke on "Psychopathology and Nutrition" at the 32nd Annual Meeting of the American Psychopathological Association in Boston, Mass, May 17-18, 1942

The American Rheumatism Association held its 9th Annual Meeting in Atlantic City, N. J, June 8, 1942. Among those who participated in the program were

Dr Charles L Short, F A C P, and Dr Walter Bauer, F A C P, Boston, Mass—"The Spinal Fluid Protein in Rheumatoid Arthritis",

Dr R Garfield Snyder, F A C P, Dr Willard Haywood Squires, F A C P, and Dr Cornelius Horace Traeger, F A C P, New York, N Y—"The Treatment of Arthritis with an Agent Containing Massive Doses of Vitamin D",

Dr Edward F Rosenberg, F A C P, and Dr Philip S Hench, F A C P, Rochester, Minn—"An Analysis of the Manner of Death Among Thirty Patients with Rheumatoid Arthritis",

Dr Charles L Steinberg (Associate), Rochester, N Y—"The Tocopherols (Vitamin E) in the Treatment of Primary Fibrositis"

The 8th Annual Meeting of the American College of Chest Physicians was held in Atlantic City, N J, June 6-8, 1942, under the Presidency of Dr Benjamin Goldberg, F A C P, Chicago, Ill Among the speakers were

Dr Robert W Keeton, F A C P, Chicago, Ill—"Adequacy of Diabetic Management in the Presence of Infection",

Charles C Hillman, F A C P, Brigadier General, (MC), U S Army—"Tuberculosis in the Army",

Robert E Duncan, F A C P, Commander, (MC), U S Navy—"Tuberculosis in the Navy"

On June 8 the American College of Chest Physicians held a joint session with the American Broncho-Esophagological Association Among the speakers at this meeting were:

Dr Louis H Clerf, F A C P, Philadelphia, Pa—"Adenoma (Mixed Tumor of the Bronchus)",

Dr Ralph C Matson, F A C P, Portland, Ore—"Bronchoscopic Aids in Chest Surgery",

Dr J Winthrop Peabody, F A C P, Washington, D C—"Bronchoscopic Aids in Medical Conditions within the Chest"

Dr Cornelius P Rhoads, F A C P, New York, N Y, spoke on "The Chemical Aspects of Cancer" at the 43rd Annual Meeting of the American Proctologic Society in Atlantic City, N J, June 7-9, 1942

Under the Presidency of Dr Milton B Cohen, F A C P, Cleveland, Ohio, the American Association for the Study of Allergy held its 20th Annual Meeting in Atlantic City, N J, June 8-9, 1942 Among the speakers were

Dr Milton B Cohen, F A C P, Cleveland, Ohio—"The Basic Relationship of Allergy and Immunity",

Dr Marion T Davidson, F A C P, Birmingham, Ala—"The Source of the Activity of House Dust"

Dr J Warrick Thomas, F A C P, Cleveland, Ohio—"Fatalities and Constitutional Reactions Following Use of Pontocaine",

Dr George E Harsh (Associate), San Diego, Calif—"Studies of Tryptic and Peptic Digestion of Extracts of Giant Ragweed Pollen"

Dr Cohen was one of the leaders at a round table discussion on "The Immunology of Allergy"

The 43rd Annual Meeting of the American Therapeutic Society was held in Atlantic City, N J, June 5-6, 1942, under the Presidency of Dr Harold S Davidson, F A C P, Atlantic City Among those who participated in the program were

Dr Harold F Robertson, F A C P, Philadelphia, Pa—"Bromide Intoxication",

Dr Nathan S Davis III, F A C P, Chicago, Ill—"Ascorbic Acid in the Treatment of Essential Hypertension—Preliminary Report",

Dr David Salkin, F A C P , Hopemont, W Va —“The Natural History of Tuberculous Tracheobronchitis”,

Dr Harry E Ungerleider, F A C P , New York, N Y , and Dr Richard S Gubner (Associate), Brooklyn, N Y —“Extrasystoles and the Mechanism of Palpitation ”

Dr Reginald Fitz, F A C P , Boston Mass , was the principal speaker at the Society's banquet Dr Fitz spoke on “Something Curious in the Medical Line ”

The American Heart Association held its 18th Scientific Session in Atlantic City, N J , June 5-6, 1942 Dr Paul D White, F A C P , Boston, Mass , President of the Association, was the principal speaker at the annual dinner Dr. White spoke on “Pioneer Days of the Discovery of Heart Disease,” and Harry G Armstrong, F A C P , Major, (MC), U S Army, delivered the George Brown Memorial Lecture on “The Effect of Flight on the Cardiovascular System ”

Among those who presented papers at the scientific session were

Dr A Wilbur Duryee, F A C P , New York, N Y —“The Present Concept of Scleroderma and Its Allied Diseases”,

Dr William Goldring, F A C P , New York, N Y —“The Reduction of Blood Pressure Associated with the Pyrogenic Reaction in Hypertensive Subjects”,

Dr Harold J Stewart, F A C P , New York, N Y —“The Effect of Cigarette Smoking on the Peripheral Blood Flow ”

Dr John E Leach (Associate), Paterson, N J , spoke on “The Effect of X-Ray Therapy on the Heart A Clinical Study” at the 27th Annual Meeting of the American Radium Society in Atlantic City, N J , June 8-9, 1942

Among the Fellows of the College who spoke at the 26th Annual Meeting of the Association for the Study of Internal Secretions at Atlantic City, N J , June 8-9, 1942, were

Dr Byron D Bowen, Buffalo, N Y —“Metabolic Changes in Coexisting Diabetes Mellitus and Addison's Disease”,

Dr Charles H Lawrence, Boston, Mass —“The Treatment of Acne with Orally Administered Estrogens”,

Dr Willard O Thompson, Chicago, Ill —“Endocrine Regulation of Growth ”

Dr Louis E Martin (Associate), Los Angeles, Calif , was chosen Vice President of the California Heart Association at its annual meeting in Del Monte, May 3, 1942

Dr George W Thorn, F A C P , has been appointed the Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, and Physician-in-Chief of the Peter Bent Brigham Hospital, Boston, Mass , to succeed the late Dr Soma Weiss, F A C P Prior to this appointment, Dr Thorn was Associate Professor of Medicine at Johns Hopkins University School of Medicine, Baltimore, Md

Dr Alvan L Barach, F A C P , New York, N Y , has been promoted to Associate Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons

Dr Wann Langston, F A C P, Oklahoma City, Okla, spoke on "Circulatory Emergencies," and Dr James William Finch, F A C P, Hobart, Okla, spoke on "Nausea and Vomiting Following Administration of Stilbestrol" at a recent joint meeting of the Custer County Medical Society and the Southwestern Oklahoma Medical Association

Dr Robert A Cooke, F A C P, New York, N Y, spoke on "The Practitioner and the Allergy Problem" at the 131st Annual Meeting of the Rhode Island Medical Society at Providence, June 3-4, 1942 Dr Charles F Gormly, F A C P, Providence, was named President of the Society

Dr John B Youmans, F A C P, Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn, delivered the annual Stuart McGuire Lectures at the Medical College of Virginia, Richmond, May 7-8, 1942 Dr Youmans spoke on "The Meaning of Nutrition" and "The Significance of Protein in the Diet"

During the session, which was conducted in cooperation with the Department of Clinical Education of the Medical Society of Virginia, the following also presented lectures

Dr Henry B Mulholland, F A C P, Charlottesville, Va — "Nutrition Problems in Postoperative Patients",

Dr Julian M Ruffin, F A C P, Durham, N C — "The Recognition of Mild or Early Vitamin Deficiencies",

Dr Maxwell R Berry, Jr (Associate), Richmond, Va — "The Significance and Treatment of Iron Deficiency Anemia"

The Canadian Medical Association held its 73rd Annual Meeting in Jasper Park, Alta, June 15-19, 1942 Among the speakers were

Dr Paul A O'Leary, F A C P, Rochester, Minn — "The Treatment of Psoriasis" and "Dermatoscleroses",

Dr Carleton B Peirce, F A C P, Montreal, Que — "Recent Improvements in the X-Ray Diagnosis of Nontuberculous Pulmonary Diseases by Means of Bronchography",

Dr W Ford Connell, F A C P, Kingston, Ont — "Digitalis, Its Uses and Misuses"

The University of Pennsylvania School of Medicine, Philadelphia, held its annual Undergraduate Medical Association Day, April 9, 1942 Dr O H Perry Pepper, F A C P, Philadelphia, Pa, spoke on "The Medical Student and the War," and Dr Carl J Wiggers, F A C P, Cleveland, Ohio, spoke on "War Gases"

Under the direction of Dr Zacharias Bercovitz, F A C P, New York, N Y, the New York Post-Graduate Medical School conducted a course on Tropical Medicine, May 25-29, 1942 Among the lecturers were

Dr Thomas T Mackie, F A C P — "Amebiasis Diagnosis, Differential Diagnosis, Treatment and Prophylaxis",

Dr Ward J MacNeal, F A C P — "Yellow Fever Diagnosis and Preventive Vaccination",

Dr Zacharias Bercovitz, F A C P — "Tropical Hygiene"

Dr Franklin G Ebaugh, F A C P , and Dr Clarke H Bainacle (Associate), both of Denver, Colo , spoke on "Fatalities Following Electric Convulsive Therapy" at the 68th Annual Meeting of the American Neurological Association held in Chicago, Ill , June 4-6, 1942

Among the speakers at the 21st Annual Meeting of the American Society of Clinical Pathologists, Philadelphia, Pa , June 4-7, 1942, were

Dr Israel Davidsohn, F A C P , Chicago, Ill —"The Rh Factor An Antigenic Analysis",

Dr Samuel A Levinson, F A C P , Chicago, Ill —"Cerebral Injuries by Mechanical Violence"

Dr Edward A Strecker, F A C P , Philadelphia, Pa , Professor and Head of the Department of Psychiatry at the University of Pennsylvania School of Medicine and President-Elect of the American Psychiatric Association, delivered the principal address at the formal dedication of the Illinois Neuropsychiatric Institute in Chicago, June 6, 1942 Dr Strecker spoke on "Neuropsychiatric Perspectives"

Dr Andrew C Ivy, F A C P , Chicago, Ill , spoke on "The Physiology of the Gall-bladder" and "The Physiology of the Thyroid Gland" at the recent Annual Spring Clinical Conference of the Pottawatomie County Medical Society, at Shawnee, Okla

Dr William H Sebiell, Jr , F A C P , Washington, D C , was elected Treasurer of the American Institute of Nutrition at its meeting in Boston, Mass , April 1, 1942

Dr Herbert T Kelly, F A C P , Philadelphia, Pa , presented a paper on "Nutrition as It Applies to General Disease," illustrated by a motion picture in natural color, at a meeting of the Gloucester County Medical Society, Woodbury, N J , May 21, 1942

The Omaha Mid-West Clinical Society will hold its 1942 meeting in Omaha, Nebr , October 26-30 The meeting will consist of local lecture periods, round table discussions, scientific and technical exhibits, and a symposium on "The Newer Concepts Regarding Hypertension and Its Treatment"

Dr Joseph T Beardwood, Jr , F A C P , Philadelphia, Pa , was named President of the American Diabetes Association at its recent meeting in Atlantic City, N J

Dr Sara M Jordan, F A C P , Boston, Mass , was elected President of the American Gastro-Enterological Association at its recent meeting in Atlantic City, N J Dr Jordan is the first woman ever to be so honored

Mr H J Cowell of Lea & Febiger, Philadelphia, Pa , has been elected President of the Medical Exhibitors Association Mr Cowell succeeds Mr C H Wantz of the General Electric X-Ray Corporation, Chicago, Ill , who had served for three terms

James O Gillespie F A C P , Colonel, (MC), U S Army, stationed at the Sternberg General Hospital, Manila, P I , has been reported missing in action

Dr Joseph H Barach, F A C P , Pittsburgh, Pa , addressed the Clearfield County Medical Society at Clearfield, Pa , on May 21, 1942 His subject was "A Clinical Consideration of Functional and Organic Diseases of the Blood Vessels"

DATES OF A C P ANNUAL SESSION ANNOUNCED

The American College of Physicians will hold its Twenty-seventh Annual Session in Philadelphia, Pa , April 13-16, inclusive, 1943 Dr George Morris Piersol of Philadelphia has been appointed General Chairman

A change will be instituted in regard to the length of the Session Heretofore the Session has opened Monday afternoon and continued through Friday afternoon Due to the War and consequent added burdens on physicians' time, as well as expenses, the 1942 Session will be condensed into four days, Tuesday through Friday The meeting will be arranged so that there will be no appreciable loss in the content of the program, members will save one day in time and expense, and by installing the exhibits on Monday, instead of over the weekend as heretofore, exhibitors will be spared double overtime labor charges

OBITUARIES

DR FREDERIC M JOHNSON

Dr Frederic M Johnson was born in New York, N Y , August 5, 1874 He received his M D degree from the Syracuse University College of Medicine in 1904, and served his internship at St Joseph's Hospital, Providence, R I , 1904-1905 From 1907-1911 he was Clinical Assistant in Diseases of the Digestive System, during 1911, Instructor, and from 1912-1917, Lecturer and Adjunct Professor of Diseases of the Digestive System, at New York Polyclinic Medical School and Hospital From 1906 until his death on April 12, 1942, he was a Member of the Staff of St John's Riverside Hospital, Yonkers, serving in various capacities, and since 1927 he was Director of Gastro-enterology at this institution He was also Gastro-enterologist at the Yonkers Professional Hospital, Consulting Gastro-enterologist at the Gray Oaks and Yonkers City Hospitals, and a Member of the Courtesy Staff of Yonkers General and St Joseph's Hospitals Dr Johnson spent the summers of 1926, 1931, 1933 and 1934 doing postgraduate work in hospitals in London and Paris

Dr Johnson was a member of the Westchester County Medical Society, the New York State Medical Society, the Yonkers Academy of Medicine, of which he was President from 1935-1936, the New York Academy of Medicine, the New York Gastro-enterological Association, the National Society for Advancement of Gastro-enterology, a Fellow of the American Medical Association, Diplomate of the American Board of Internal Medicine He became an Associate of the American College of Physicians in 1925 by virtue of his membership in the American Congress on Internal Medicine

Dr Johnson was a member of Masonic Lodge, Past Master of Nepperhan Lodge, member Terrace City Chapter, Yonkers Commandery and Mecca

Temple of New York He was a Director of the Yonkers Savings and Loan Association and a Vestryman at St Andrew's Memorial Church

Dr Johnson is survived by his widow and two daughters

CHARLES F TENNEY, M D , F A C P ,
Governor for Eastern New York

DR ARCHIBALD ADDISON ALEXANDER

Dr Archibald Addison Alexander, F A C P , of Oakland, Calif , died at his home on January 17, 1942 Dr Alexander was a native Californian, as he was born at San Ramon, Calif , May 28, 1880 After graduating from high school in his native community, he attended the University of California, receiving his A B degree in 1902, and his M D degree from the University of California Medical School in 1907 He was an Instructor in Medicine at the Oakland College of Medicine from 1908-11 He became an Associate in Medicine at the Samuel Merritt Hospital, Oakland, in 1912, and served until 1931, when he became Chief Cardiologist to the Hospital He was also Cardiologist to the Peralta Hospital of Oakland He served as an Associate in Medicine at the Alameda County Hospital from 1928 until his death He was also Consultant in Cardiology at the Children's Hospital of the East Bay

Dr Alexander was a Diplomate of the American Board of Internal Medicine, a member of the Alameda County Medical Society, the California State Medical Association, the California Academy of Medicine and the American Medical Association He became a Fellow of the American College of Physicians in 1935

Although interested in cardiology, Dr Alexander was a keen student in the entire field of internal medicine and a firm believer in a broad base for specialization He was a consistent, diligent worker, very faithful and loyal to the institutions he served, never seeking or asking praise or reward

ERNEST H FALCONER, M D , F A C P ,
Governor for Northern California

DR JULIUS PETER DWORETZKY

Dr Julius Peter Dworetzky of Liberty, New York, was born December 24, 1885, in Lido, Russia, and died April 20, 1942

In 1910 Dr Dworetzky received his M D degree from the Long Island College Hospital and served his internship in this hospital from 1910-12 From 1913-18, Dr. Dworetzky was Resident Physician at the Municipal Sanatorium, Otisville, N Y., and later became Visiting Physician He served as Consulting Physician, Ulster County Tuberculosis (Kingston), St Francis (Port Jervis), Elizabeth A Horton Memorial (Middletown), and St Clare's (New York City) Hospitals, he was Visiting Physician,

Maimonides Hospital, Liberty, and was Medical Examiner for the Veterans Administration. A few years ago he became Director of Medicine at the Municipal Sanatorium.

During World War 1, Dr Dworetzky served as a Captain with the American Red Cross and with the Rockefeller Commission for the Control of Tuberculosis in France.

Dr Dworetzky was a member of the New York State Medical Society, the National Tuberculosis Association, the American Laryngological, Rhinological and Otological Society, the American College of Chest Physicians, a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine and the American Board of Otolaryngology, and a Fellow of the American College of Physicians since 1931.

Dr Dworetzky made several original contributions to the literature in the field of laryngeal tuberculosis.

CHARLES F TENNEY, M D , F A C P ,
Governor for Eastern New York

MINUTES OF THE BOARD OF REGENTS

ST PAUL, MINN

APRIL 19, 1942

The first meeting of the Board of Regents, in conjunction with the Twenty-sixth Annual Session of the American College of Physicians, convened in the Municipal Auditorium, St Paul, Minn, Sunday afternoon, April 19, 1942, at 2 30 p m, with President Roger I Lee presiding and Mr E R Loveland acting as Secretary, and with the following members in attendance

Roger I Lee	<i>President</i>
James E Paullin	<i>President-Elect</i>
Thomas T Holt	<i>Second Vice-President</i>
William D Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary-General</i>
Francis G Blake	
Reginald Fitz	
William J Kerr	
Charles T Stone	
J Morrison Hutcheson	
T Homer Coffen	
Ernest E Irons	
Jonathan C Meakins	
Charles H Cocke	
John A Lepak	<i>General Chairman</i>
E R Loveland	<i>Executive Secretary</i>

At this point President Lee introduced Dr Lepak, the General Chairman of the St Paul Session, whereupon Dr Lepak made various announcements in regard to the clinics, hotels, transportation facilities and other matters affecting the meeting

The Secretary read abstracted Minutes of the preceding meeting of the Board of Regents, December 14, 1941, which, by resolution, were approved as read

President Lee called for communications

Secretary Loveland then read communications from Drs Samuel E Munson, James D Bruce, M C Pincoffs, D S Lewis and David Barr, members of the Board of Regents who were prevented from being present Among other communications presented by the Secretary were the following

- (1) A letter from the Radiological Society of New Jersey, containing a resolution affirming that that Society has gone on record as being unalterably opposed to an all inclusive hospital service plan including medical, x-ray and laboratory services
- (2) A letter from the Office of the Surgeon General of the Army concerning contemplated training programs in certain fields of specialty and for the allotment of officers to various postgraduate courses and clinics
- (3) A letter from Dr Virgil E Simpson, F A C P, Louisville, Ky, concerning activities of the College in connection with the U S Pharmacopoeia, standardization of hospitals, nomenclature of diseases and other services
- (4) A formal report from Dr Charles F Tenney, F A C P, official College delegate and spokesman for the College delegation to the U S Pharmacopoeial Convention as follows

"A meeting of the Medical-Pharmaceutical Convention took place at the Hotel Statler, Cleveland, Ohio, on April 6, 1942, under the auspices of the Joint Committee of the American Medical Association and the American Pharmaceutical Association. Drs Charles F Tenney, Edward G Spalding and Torald H Sollmann were the delegates from the American College of Physicians.

"The afternoon of April 6 was given over to the reading of papers and a most excellent paper was given by Dr Howard Dietrick, of Cleveland, on the 'Evolution of the Apothecary'. From an historical standpoint it was excellently presented, starting from the earliest periods, B C, and carrying them on up to the present time. Dr E F Kelly, Chairman of the Board of Trustees of the United States Pharmacopoeial Association and Secretary of the American Pharmaceutical Association, traced out very clearly the 'Trends of Pharmaceutical Practice,' stating the total number of Pharmaceutical Schools and the number of men graduated from these schools each year. He also stated that he hoped very soon they would have practical courses following their graduation, similar to internships in hospitals which would extend for a period of about two years. The third paper, 'Is the Program of Pharmaceutical Education Justified?', was given by Dr Robert C Wilson, Dean of the School of Pharmacy of the University of Georgia, Athens, Georgia. This paper explained how justified was the interest taken in the progress for pharmaceutical education and that it had been warmly adopted by the different schools of pharmacy in the different universities throughout the United States. Dr Torald H Sollmann, F A C P, Dean, Professor and Director of the Department of Pharmacology and Materia Medica, Western Reserve University School of Medicine, was the presiding officer for the afternoon meeting, and general discussions followed the reading of the papers. Among the speakers was Dr Morris Fishbein, Editor of the American Medical Association, who seemed to carry the impression that the pharmacists would eventually have to rely upon hospitals and other institutions rather than preparing their prescriptions in drug stores. He thought the combining of a restaurant and a drug store was bad practice and for that reason pharmacy was being pushed backward rather than forward. The meeting was adjourned at 5:30 p m.

"The evening session opened at 6:30 p m with a dinner which was largely attended by the members present, Dean B V Christensen, presiding.

"The address of the evening was given by Dr Fishbein on 'Status of Medicine and Pharmacy in the War—and After'. He talked rapidly and fluently for about forty-five minutes, using about one hundred and fifty words per minute. He stated that this was the first joint meeting in history of representatives of the American Medical Association and the American Pharmaceutical Association. He gave a most excellent discussion not only with regard to his title, but also recommended that the Medical Procurement and Assignment Service, which is making an inventory of all persons practicing medical, dental, or veterinary professions, should extend its services to include 'the correlated pharmaceutical profession, physical therapists, laboratory specialists, and roentgenological technicians. By suitable collaboration of this agency with the National Roster of Scientific and Trained Personnel,' said Dr Fishbein, 'we will be able to meet more adequately the needs of our fighting forces'.

"Dr Fishbein told of the recent appointment of an advisory committee on drugs and supplies of the division of medical sciences of the National Research Council. It was thought not long ago, he said, that this nation had a three year supply of such drugs as quinine and morphine, but that estimate did not take into account the entrance of troops into areas where contact was made with such diseases as leishmaniasis, kala azar, African sleeping sickness and yellow fever.

"The evening meeting adjourned about 9 30 p m The above papers will no doubt be published in the near future, and any of the Fellows who are interested may obtain copies if they write to Dr Cary Eggleston, President of the United States Pharmacopoeial Convention, 125 East 74th Street, New York City

"The Adjourned Session of the 1940 Decennial Meeting of the United States Pharmacopoeial Convention, reconvened at the Hotel Statler, Cleveland, Ohio, on April 7, 1942, with Dr Cary Eggleston, President, in the Chair

"After the meeting was called to order, Dr Morris Fishbein requested to be recognized He moved that inasmuch as no changes could be made in the Proposed Constitution until 1950 that no discussion of the Constitution take place at this time It was seconded and carried

"However, the By-Laws and their changes could be acted upon at this meeting, so each chapter and article of the By-Laws was read, voted upon, changes made, and finally adopted as the By-Laws governing the Pharmacopoeial Convention It was then voted to read the new Constitution This was done but no comments or discussions were permitted The changes that have been made in the By-Laws were circulated in typewritten form and copies will be available for distribution to the members probably within a short time All this work had been compiled and brought up to date under the guidance of legal advisers

"The Committee on Revision of the U S Pharmacopoeia stated that the U S P No XII could be ready for distribution by July 1, 1942 Circulars were distributed in typewritten form of articles advised for the U S P No XII with Latin and English titles There was some discussion as to the shortage of drugs because of inability to get them and also the large amount which are taken and sent to our forces over-seas. The meeting adjourned at 12 40 p m "

Respectfully submitted,

(Signed) CHARLES F TENNEY

Delegates CHARLES F TENNEY, *Chairman*

EDWARD G SPALDING

TORALD H SOLLMANN"

SECRETARY LOVELAND During the past year a movement was started to greatly reduce the number of medical agencies represented in the U S Pharmacopoeial Convention, in fact, to eliminate practically all societies, including the American College of Surgeons and the American College of Physicians, but to retain the American Medical Association and its constituent state medical societies It was not entirely clear whether or not this movement was directed against some of the special societies which held membership, but there have been many who felt that this College should retain its representation, because there is no group of physicians that has a more definite interest and part both in prescribing and teaching in this important field Dr Tenney, as spokesman, represented the College and its interests and his report reveals there will be no change in the next eight years I would suggest, however, that this report be incorporated in the minutes and published

PRESIDENT LEE If there are no objections it will be so ordered

The next item of business will be the appointment of a member of the American Board of Internal Medicine for the term 1942-45 The President was advised that the term of Dr. David P Barr would expire June 30, 1942 . It is found that Dr Barr has served only one full term and can be reelected to the Board

DR WILLIAM D STROUD. I move that Dr Barr's name be recommended for re-appointment to the American Board of Internal Medicine for the next three years

DR GEORGE MORRIS PIERSON: I second Dr Stroud's motion recommending the re-appointment of Dr Barr

PRESIDENT LEE. . . All those in favor of recommending to the American Board of Internal Medicine the name of Dr David P Barr, of New York, as the repre-

sentative of this College on the American Board of Internal Medicine for the term 1942-45 will say "aye", opposed "no"

The motion was carried

PRESIDENT LEE The next item of business is the report of the Secretary-General

DR GEORGE MORRIS PIERSOL, *Secretary-General* Since the last meeting of the Board 16 Fellows and 2 Associates have been lost by death, namely

Fellows

Austin, Albert Elmer, Old Greenwich, Conn , January 26, 1942
 Cutter, William Dick, Chicago, Ill , January 22, 1942
 Helm, Jesse Bundren, M C , U S Navy, November 26, 1941
 Jones, Louise Taylor, McLean, Va , December 21, 1941
 Lambert, Samuel Waldron, Sr , New York, N Y , February 9, 1942
 Leech, Frank, Washington, D C , February 4, 1942
 Marbury, Charles Clagett, Washington, D C , December 10, 1941
 Niles, Walter Lindsay, New York, N Y , December 22, 1941
 * Peters, LeRoy Samuel, Albuquerque, N M , December 17, 1941
 Reque, Peter Augustin, Brooklyn, N Y , December 4, 1941
 Ryan, William Joseph, Pomona, N Y , February 20, 1942
 Sleyster, Rock, Wauwatosa, Wis , March 7, 1942
 Stoddard, Charles Hatch, Milwaukee, Wis , December 17, 1941
 Sylvester, Charles Bradford, Portland, Maine, December 18, 1941
 Tracy, Martha, Philadelphia, Pa , March 22, 1942
 Weiss, Soma, Boston, Mass , January 31, 1942

Associates

Fisler, Harry Cattell, Easton, Pa , February 20, 1942
 Wolf, Isadore Julius, Kansas City, Mo , December 17, 1941

This brings the total since the last Annual Session to 48 Fellows , 5 Associates, total, 53 Comment for the preceding year, 47 Fellows , 7 Associates, or a total of 54 died

The following twelve additional Life Members are also reported since the last meeting of this Board

Siegfried Block, Brooklyn, N Y
 William Hall Bunn, Youngstown, Ohio
 F Gorham Brigham, Brookline, Mass
 Samuel Lee Gabby, Elgin, Ill
 George Curtis Crump, Asheville, N C
 Henry L Ulrich, Minneapolis, Minn
 Edward William Hayes, Monrovia, Calif
 Frederick Edward Hudson, Stamford, Tex
 H Leon Jameson, Philadelphia, Pa ,
 James D Bruce, Ann Arbor, Mich
 Ardrey W Downs, Edmonton, Alta , Canada
 Maurice Lewison, Chicago, Ill

At the preceding meeting of this Board, the Secretary-General reported 4 new Life Members, which makes a total since the last Annual Session of 16, a grand total of 183, of whom 17 are deceased, leaving a balance of 166

PRESIDENT LEE This is a report to the Board of Regents and requires no action I now call for the report of the Committee on Credentials The list of recommendations to be presented is already in your hands

* Governor for New Mexico

DR GEORGE MORRIS PIERSOL, *Chairman* The Committee on Credentials has met twice since the preceding Regents' meeting, once in Philadelphia on March 22, 1942, and again at St Paul on April 19, 1942 In your hands is a typewritten list of candidates who are recommended for election to Fellowship and Associateship The following is an analysis of the candidates considered on March 22

A *Candidates for FELLOWSHIP*

Recommended for election		
Advancement from Associateship	103	
Direct election to Fellowship	14	117
	<hr/>	
Elect Associate First		1
Deferred for Further Investigation, Maturity, etc		15
Rejected		1
		<hr/>
		134

B *Candidates for ASSOCIATESHIP*

Recommended for Election		76
Deferred for Further Credentials		9
Rejected or Withdrawn		9
		<hr/>
		94

An analysis of the candidates considered on April 19 is as follows

A *Candidates for FELLOWSHIP*

Recommended for election		
Advancement from Associateship	46	
Direct election to Fellowship	2	48
	<hr/>	
Deferred for Further Investigation, Maturity, etc		10
Rejected		1
		<hr/>
		59

B. *Candidates for ASSOCIATESHIP*

Recommended for Election		44
Deferred for Further Credentials		0
Rejected or Withdrawn		5
		<hr/>
		49

Chairman Piersol presented each group individually, discussing special cases, and on his motion, seconded and carried, the entire list was elected with a covering resolution as follows.

RESOLVED, that the following list of 165 candidates be and herewith are elected to Fellowship in the American College of Physicians (ED NOTE This list was published in the May, 1942, issue of this journal)

RESOLVED, that the following list of 120 candidates be and herewith are elected to Associateship in the American College of Physicians (ED NOTE This list was published in the May, 1942, issue of this journal)

DR PIERSOL *Chairman* Several other matters came before the Committee for consideration. The first is a report on candidates elected to Associateship on April 18,

1937, whose period of probation has now expired. Seven Associates elected at that time have not presented their credentials, or their credentials have not been accepted, and, therefore, are herewith recorded as dropped under provisions of the By-Laws.

A final analysis of the disposal of the Associates elected April 18, 1937, is as follows:

Advanced to Fellowship	112
Dropped for Failure to Qualify or to Present Credentials	7
Resigned	0
Deceased	0
	<hr/>
	119

Every reasonable effort has been made to influence Associates to qualify for Fellowship, and if they have failed to do so it has been due to their own indifference or carelessness.

A formal resolution offered by Dr. Piersol, seconded by Dr. Cocke, and carried, confirmed the dropping of the seven Associates in accordance with the provisions of the By-Laws.

DR PIER SOL, *Chairman*. The Committee recommends to the Board of Regents that Dr. Richard H. Dalrymple be reinstated to Fellowship.

On motion by Dr. Stroud, seconded by Dr. Kerr and regularly carried it was resolved that Dr. Richard H. Dalrymple, Fond du Lac, Wisconsin, be herewith reinstated to Fellowship in the American College of Physicians.

President Lee announced that since Dr. Paullin and Dr. Morgan, Chairmen of the Committee on Public Relations and Advisory Council on Medical Education, respectively, had not yet arrived, their reports would be delayed until the next meeting. He called upon Dr. Blake as Chairman of the Committee on Fellowships and Awards for reports.

DR FRANCIS G. BLAKE. I submit a report of the Committee on Fellowships and Awards. Of the three Fellowships awarded by the American College of Physicians at the meeting of the Board of Regents on December 14, 1941, two were accepted as follows:

1. Dr. James Hopper, Jr., to begin work September 1, 1942, in the Department of Internal Medicine, Yale University School of Medicine, under the direction of Dr. John P. Peters, on "A Comparison of the Carbon Monoxide and Dye Methods of Blood Volume Determination."
2. Dr. Joseph L. Lilienthal, Jr., to begin work September 1, 1942, in the Department of Medicine, Vanderbilt School of Medicine, under the direction of Dr. E. M. Harvey on "A Study of Myasthenia Gravis and Related Problems in Neuromuscular Transmission in Man."

The third award to Dr. Charles P. Emerson, Jr., was declined because of military service. Following Dr. Emerson's declination of the fellowship, award was made to the alternate, Dr. Carl G. Heller, to begin work July 1, 1942, at Wayne University College of Medicine, under the direction of Dr. Gordon B. Myers on the physiology of hypo- and hypergonadism in relation to hypo- and hyperpituitarism in human males and females.

Dr. Allen D. Bass, one of the American College of Physicians' fellows for the current year, tendered his resignation effective January 1, 1942, to engage in a war research project, and his resignation was accepted.

Respectfully submitted,

FRANCIS G. BLAKE, M.D., *Chairman,*
Committee on Fellowships and Awards

On motion by Dr Blake, seconded by Dr Meakins and regularly carried this report was adopted

PRESIDENT LEE Do you have a further report to make, Dr Blake?

DR BLAKE I attended the meeting of the Advisory Council on Medical Education in Chicago on February 15 It was a relatively brief meeting, the discussion being largely concerned with the acceleration of the medical school course, the adjustment of internships to the accelerated program, and problems arising from conflict with various state laws relative to the required length of medical education

Only two actions were taken one, a vote expressing appreciation of the cooperation of Selective Service and the Surgeons General, in their collaboration with the Committee on Preparedness of the Association of American Medical Colleges in working out a satisfactory adjustment which will permit medical students to complete their education, two, an endorsement of certain actions of the Association of American Medical Colleges relative to the accelerated program of medical education, as follows that there should be no lowering of requirements for admission to the medical schools because of the accelerated program, that the Executive Council of the Association shall negotiate with the Federal Bureau of Education with respect to the possibility of obtaining loans for medical students who may need additional financial assistance because of inability to work during the summer months, that the length of internships be not reduced below twelve months

PRESIDENT LEE This report requires no action It will be placed on file

Dr Fitz, will you report for the Committee on the ANNALS OF INTERNAL MEDICINE?

DR REGINALD FITZ Mr President, the Editor, Dr M C Pincoffs, has been called to active service It has been the feeling of the Committee on the ANNALS that it would be proper for the Committee to recommend to the Board of Regents that the Editor be given leave of absence during whatever time he may be away in order that his service as Editor may be obtained when he returns We make that recommendation

The second point that comes up concerns what may be done during his absence The Editor communicated with the Chairman, and the Chairman with the President I am informed that tentatively the editorial work of the ANNALS has been left in the hands of Dr Paul Clough, Assistant Editor, until this matter is officially settled

Dr Clough is perfectly competent and well trained to take care of the editorial work While Dr Pincoffs is away an Assistant Editor should be appointed to work under Dr Clough, and in that way the continuous policy of the ANNALS can be maintained

Dr Pincoffs has already submitted the name of an Assistant Editor to the Committee on the ANNALS for consideration, but such nomination has not been submitted to me Dr Pincoffs reports that the affairs of the ANNALS appear to be in good order The Editor's office has on hand a large amount of very good material, so that if the output of scientific work falls off in the near future there will still be a good deal of material in the Editor's hands, as a backlog, for several months to come

And, finally, Dr Pincoffs wishes very much to extend to the Committee and to the Regents his appreciation of their support through the years he has been Editor He feels that to leave the ANNALS in the hands of Dr Paul Clough is the best available solution and he hopes that the periodical will continue while he is away

I should like to make a motion that Dr Pincoffs be given a leave of absence

DR MEAKINS I second the motion

DR STROUD May I ask, Mr President, if there is to be any new arrangement made concerning the salary to be paid to the Editor, or whether that automatically, in the present amount shall go to Dr. Clough?

DR FITZ In Dr Pincoffs' letter to Dr Palmer, Chairman of the Committee, the understanding was that Dr Clough, if his appointment is confirmed by the Board of

Regents, will be in charge of the ANNALS during Dr Pincoffs' absence and will receive the same salary as Dr Pincoffs had been receiving, and that the Assistant Editor shall receive the same salary Dr Clough previously received. Therefore, the budgetary arrangement will remain constant.

PRESIDENT LEE We have been very fortunate, indeed, to have Dr Clough available as Acting Editor. Are there any other questions? The first motion concerns an indefinite leave of absence to Dr Pincoffs as Editor. All those in favor will say "aye", opposed "no."

The motion was carried.

DR FITZ I move that Dr Paul Clough be appointed by the Board of Regents as Acting Editor during Dr Pincoffs' absence at the same salary which Dr Pincoffs previously received.

The motion was seconded by Dr Meakins and unanimously carried.

On motion by Dr Cocke, seconded by Dr Stroud and regularly carried it was resolved that Dr Paul Clough as Acting Editor shall be empowered to nominate an Assistant Editor to the Committee on the ANNALS OF INTERNAL MEDICINE for official approval.*

PRESIDENT LEE The Executive Secretary will report on increased printing charges for the journal.

SECRETARY LOVELAND Beginning July 1, 1942, the printers request permission to make an additional charge of \$2.65 per form of 32 pages, per thousand copies, which will amount to approximately \$90.00 per issue, and also permission to increase cost by approximately \$4.50 per issue for cover stock. These two increments will amount to approximately \$1,100.00 to \$1,200.00 per annum. Since our original printing contract was authorized by the Regents, I believe this alteration should be first approved by the Regents and herein recorded.

On motion by Dr Meakins, seconded by Dr Cocke, it was resolved that the printing contract of the Lancaster Press be altered in the form and amount suggested by the Executive Secretary.

Dr Ernest E. Irons, Chairman, American Board of Internal Medicine, distributed several charts showing results of examinations, relative ages and other matters of interest in the experience of that Board in conducting its work. He referred to the probability of some lean years in the near future, due primarily to the war.

DR ERNEST E. IRONS About a year ago the American Board of Internal Medicine discussed with the Board of Regents of the College a reduction in the examination fee, but at that time felt that in view of the added expense for examination in sub-specialties, it would be well to wait one year for results. Our experience now indicates that receipts from sub-specialties' examinations have been just about enough to cover the expenses. However, we are now prepared to consider the reduction of the examination fee from \$40.00 to \$30.00, and \$10.00 for certification, making a total expense of \$40.00 instead of \$50.00, provided the College cares to consider this program.

Our fee for examination is far lower than that of most of the other special Boards, but the volume that we have to handle makes possible the consideration of reduction.

PRESIDENT LEE You make no motion, Dr Irons, you simply desire a discussion on this matter?

DR IRONS The Board of Regents brought this matter up a year ago, asking the American Board of Internal Medicine to make some reduction. If the Regents desire to make a reduction in the examination fee, the American Board of Internal Medicine is now in a position to go along.

*N.B.—Subsequently Dr W. Halsey Barker, of Baltimore, was formally appointed Assistant Editor beginning May 1, 1942, Dr Clough assumed the title of Acting Editor on May 1, 1942.

DR WILLIAM J KERR Dr Irons, there is a reserve of about \$27,000 in your Treasury, and a gain of \$4,000 during the past year in spite of the sub-specialty Board examinations. It seems to me that the College and the Board could combine in making some reduction in fees for the candidate, and this would be a wise move. Whether or not other specialty Boards do this, I think ours should take the lead.

DR GEORGE MORRIS PIERSOL Mr President, the Finance Committee should carefully consider this and bring in a report on its advisability.

DR CHARLES H COCKE Mr Chairman, it seems to me that in view of the situation that is going to involve a great many men now, we want to act very carefully. Dr Piersol suggested that this should receive, accordingly, a careful examination. There is going to be considerable pressure for the reduction of College fees. This has already been brought to my attention as a Governor, and I recommend the proper study of this problem by the Finance Committee.

DR IRONS Mr. Chairman, we are all aware that the reduction Dr Cocke points out involves also other things, and we are now talking about the amount the man pays for admission. Pressure on the College is going to be on the amount he pays after he is admitted.

SECRETARY LOVELAND Is there any variation in the examination fee for different classes of physicians, such as those on active service or otherwise?

DR IRONS No.

PRESIDENT LEE The Chairman of the Finance Committee, Dr Pepper, is not present. At the last meeting the Finance Committee was prepared to be liberal in the treatment of those who are called to active service, but found itself in a quandary as to reducing annual dues of temporary officers below the annual dues of those who are officers of the armed forces permanently. Furthermore, there are going to be more people employed by the Government. That too has been carefully considered by the Finance Committee, and this preferential list for a low fee, lower than that established for the present regular officers of the Army and Navy, put the Finance Committee in a great deal of a quandary. The Board of Regents did vote that when a man enters on active service his fees shall be the same as for those in the regular medical corps of the Army and Navy.

I received a letter from Chairman Pepper who merely stated that as of the that Committee he was prepared to be as liberal as possible to these temporary members of the armed forces, but that it seems difficult to find a satisfactory solution.

DR WILLIAM D STROUD Mr President, I move that since the Finance Committee is reporting at the Tuesday afternoon session of this Board, that we confer with Dr. Irons and bring in a recommendation for consideration to the Regents.

The motion was seconded by Dr Paulin and unanimously carried.

There being no further business, President Lee read various announcements and the meeting adjourned at 4 20 p m.

Attest (Signed) E R LOVELAND,

Secretary

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DIAGNOSTIC CRITERIA FOR SUBPHRENIC ABSCESS BASED UPON A STUDY OF 139 CASES *

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IN reviewing the literature on subphrenic abscess, one is confronted by a host of terms used more or less synonymously with subphrenic abscess. The more frequently encountered names are perigastric abscess (Barlow), suprahepatic abscess (Beinheim), supracolic abscess (Mitchell), false pneumothorax (Cossy), pneumoperforative peritonitis (Sanger), hepatoperitoneal abscess (Ferol), pyopneumothorax subphrenicus (Leyden), subphrenic empyema, hypophrenic empyema, subphrenic pyopneumo-peritonitis, subphrenic peritonitis, subdiaphragmatic peritonitis and subdiaphragmatic abscess.

Delario¹ states that the first case of subphrenic abscess described in the literature was reported in 1824. This was based on the necropsy observations of a case of apparently long duration. Some 20 years later Barlow² reported clinical observations of a patient who developed this complication after perforation of the stomach.

Because of the somewhat dissimilar symptom complex, physical signs, etc., produced by differences in the location of these abscesses, it would not be amiss to present a brief description of the anatomy of the area involved with reference to the various possible locations of these abscesses. The following anatomical account is based upon the studies of Martinet,³ Box and Eccles,⁴ and Barnard.⁵ The subphrenic area is bounded above by both diaphragms and below by the transverse colon and its mesentery. This area is further divided into two main regions, an intraperitoneal area and an extra-peritoneal area. The liver divides the intraperitoneal area into a suprahepatic area and an infrahepatic, each of which is composed of three smaller limited areas (figure 1).

The Suprahepatic Intra-peritoneal Area This area is composed of (1) the right anterior suprahepatic area located above the liver, to the right of

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the coronary ligament and in front of the right lateral ligament, (2) the right posterior suprahepatic area, located above the liver and behind the right lateral ligament, and (3) the left suprahepatic area located above the liver and to the left of the left lateral ligament, which in turn is a prolongation to the left of the coronary ligament

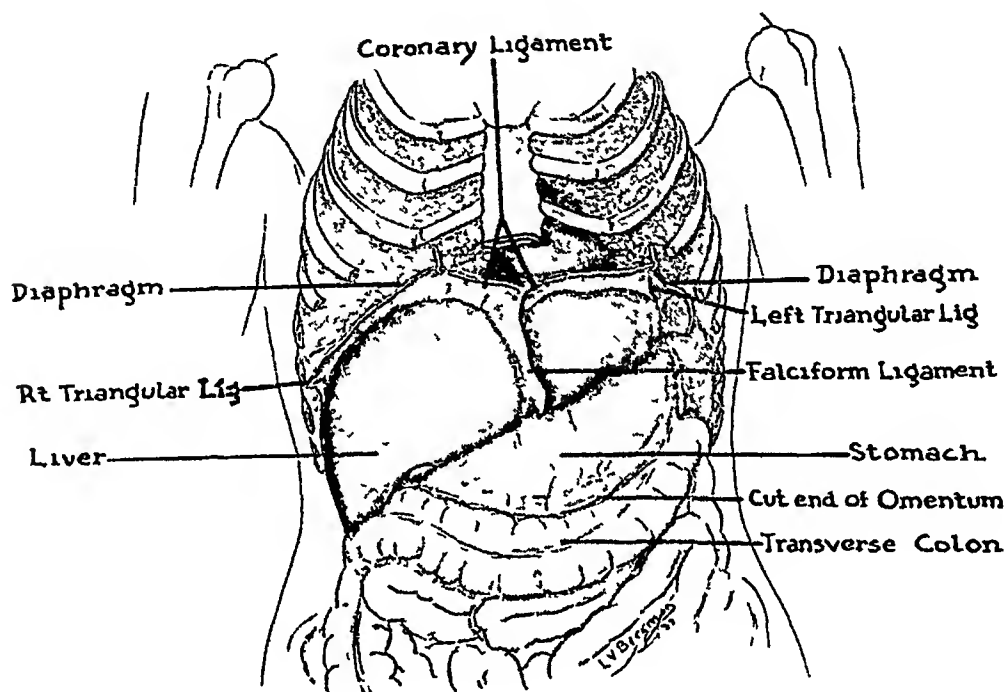


FIG. 1 An anterior view of the diaphragmatic area exposing the subphrenic region

The diaphragm is elevated anteriorly to expose the suprahepatic area. The great omentum is cut away from the stomach to expose the transverse colon. The subphrenic area is bounded above by the diaphragm and below by the transverse colon and its mesentery.

The Intrahepatic Intra-peritoneal Area This area is composed of three lesser and limited areas, namely (1) the right infrahepatic area, located below the liver and to the right of the round ligament of the liver and the ligament of the ductus venosus, (2) the left anterior infrahepatic area, located below the liver and to the left of the round ligament and the ligament of the ductus venosus and in front of the stomach, and (3) the left posterior infrahepatic area located below the liver and to the left of the round ligament and the ligament of the ductus venosus and behind the gastrohepatic omentum.

The Extraperitoneal Area This area is composed of (1) The anterior extraperitoneal area, located between the anterior external surface of the peritoneum and the internal surface of the upper anterior abdominal

wall below the diaphragm. This area may be arbitrarily subdivided into a right and left side by a midabdominal line. (2) The right posterior extraperitoneal area, located between the posterior external surface of the parietal peritoneum and the upper posterior abdominal wall below the diaphragm and to the right of the inferior leaf of the coronary ligament. This area includes the bare area of the liver. (3) The left posterior extraperitoneal area, located between the posterior external surface of the parietal peritoneum and the upper posterior abdominal wall below the diaphragm and to the left of the inferior leaf of the coronary ligament.

ETIOLOGY

Subphrenic abscess is rarely a primary condition, its presence almost always suggests a suppurative process elsewhere in the body, and generally one within the abdomen. Although uncommon, it may occur after pneumonia, empyema, furunculosis, osteomyelitis of the vertebrae, septicemia, etc. The subphrenic space may become infected through any of six routes:

(1) *By direct extension* from the peritoneum and contiguous organs—liver, stomach, duodenum, kidney, gall-bladder, spleen, pancreas, biliary ducts, osteomyelitis of the lower dorsal or upper lumbar vertebrae, etc.

(2) *By distant extension*—an appendiceal infection, a pelvic infection, diverticulitis of the colon, infection about the urinary bladder, an infection of the skin on the upper part of the abdomen or lower part of the thorax, etc.

(3) *By rupture into the subphrenic area*—abscess of the liver, ulceration of the cardio-esophageal region, hydatid disease of the liver, osteomyelitis of the vertebrae or ribs, empyema thoracis, etc.

(4) *By retrograde lymphatic extension*—empyema thoracis, pneumonia, lung abscess, mediastinitis, etc.

(5) *By direct implantation* or injury to an anatomically related organ following a penetrating injury.

(6) *By metastatic infection* as in cases of furunculosis, septicemia, influenza, osteomyelitis, etc.

The methods whereby these infections reach the subphrenic space have been discussed elsewhere.⁶ The reader is referred to this article for a detailed description.

Of the 139 cases reviewed in this study, 44 were due to primary disease in the liver and biliary passage, 29 to lesions in the appendix, nine to renal disease and eight to disease of the stomach and duodenum (table 1). It is of interest that of the cases secondary to disease of the liver and biliary passages, four were secondary to liver abscesses and 16 followed disease of the biliary passages which was accompanied by localized peritonitis at the time of surgical operation on the biliary tract. It is also worthy of note that about two-thirds of the subphrenic abscesses which followed lesions in the

TABLE I

Etiologic Causes of 139 Subphrenic Abscesses

Organ	Number of Cases
Liver and biliary passages	44
Appendix	29
Kidney	9
Stomach and duodenum	8
Pelvic infections (abscess)	6
Grip	4
Female genitalia	3
Pneumonia	3
Empyema	2
Furunculosis	2
Spinal disease	2
Prostatic abscess	2
Intestine	1
Abscess of the lung	1
Unknown causes	23

appendix were associated with generalized peritonitis. Of the eight cases due to gastroduodenal causes, seven were accompanied by perforations and one was due to duodenitis. Before presenting the clinical aspects of this condition, it should be pointed out that all subdivisions of the subphrenic area are not equally susceptible to infection (table 2). Consulting this table, we note that the four areas most commonly infected are (1) the right infrahepatic intraperitoneal space, in 35 cases, (2) the right posterior suprahepatic intraperitoneal space, in 22 cases, (3) the right anterior suprahepatic intraperitoneal space, in 16 cases, and (4) the right posterior extraperitoneal space, in 12 cases.

CLINICAL FEATURES

From the foregoing, it can be seen quite readily that clinical manifestations are varied and will not be the same in all cases. A difference in etiology, in the age of the patient, or the location of the abscess coupled with the co-existing condition responsible for the subdiaphragmatic infection and any other complications present, will tend to alter the clinical aspects. Regardless of the influences these factors may have upon the origin of a subphrenic abscess, the mode of onset in all cases will take any of four characteristic forms: (1) sudden, (2) insidious, (3) postoperative, or (4) recurrent.

Sudden Onset. In such instances the onset may simulate a ruptured peptic ulcer (more commonly gastric) with an acute generalized peritonitis. In these cases there is a history of acute abdominal (epigastric) pain, nausea, vomiting, prostration, difficulty in taking a deep breath, pain in the lower thoracic region, a sensation of fullness in the upper part of the abdomen and tenderness in the epigastric, infracostal or costophrenic region. In the early stages of the disease the patient may be in shock. Later, signs and symptoms of infection may become manifest. There were 23 cases (16.5 per cent) in this series in which the onset was sudden.

TABLE II

Source of Infection of the Various Divisions of the Subphrenic Space and the Incidence of These Infections in 118 of the Author's Cases

Location	Etiology	No of Cases	Percentage
Right posterior suprahepatic intraperitoneal space	Right diaphragm and pleura, pyloroduodenal region, paracolic gutter, draining appendix, cecum, pelvis, etc., right infrahepatic area	22	18.5
Right anterior suprahepatic intraperitoneal space	Pyloroduodenal region, gall-bladder	16	13.5
Right infrahepatic intraperitoneal space	Liver, gall-bladder and biliary ducts, hepatic flexure of colon, pyloroduodenal region, right posterior suprahepatic area	35	29.7
Left suprahepatic space	Gastro-esophageal region	1	0.8
Left anterior infrahepatic space	Perforation of the anterior wall of stomach, liver and spleen	3	2.5
Left posterior infrahepatic space	Perforation of the posterior wall of stomach, pancreatitis and infected pancreatic cysts, spleen, leakage from a retrocolic gastroenterostomy anastomosis, perforation of a gastrojejunal ulcer	5	4.2
Right posterior extraperitoneal space	Infection of bare area of liver, retrocecal appendix, right perinephric abscess, pancreatitis, suppuration of right lumbar and iliac glands, right side of thorax and diaphragm	12	10.2
Left posterior extraperitoneal space	Left perinephric abscess, diverticulitis of descending colon, suppuration of left lumbar and iliac glands, descending colon, pancreas, left side of thorax and of diaphragm	5	4.2
Left anterior extraperitoneal space	Lymphatics of the round ligament of the liver, lymphatics of the sheath of the rectus muscle, infections of abdominal wall	1	0.8
More than one space infected		6*	5.1
Infected space not determined		12	10.2

* These cases were not included in the table

Insidious Onset When the onset is insidious, the symptom complex is subacute and simulates that of an obscure intra-abdominal lesion such as a chronic cholecystitis or a mild mesenteric lymphadenitis. At first the symptoms are those of vague upper abdominal discomfort without distinct localization. Later, the patient complains of pains and aches in the lower posterior thoracic region or in the flank. At times the pain may radiate to the shoulder or along the infracostal region. The pain is aggravated by deep breathing, sneezing or coughing. The symptom complex is progressive and sooner or later signs and symptoms of infection become manifest.

It is in this group of cases particularly that a tumor mass may be encountered. There were 40 cases (29 per cent) in the present series in which the onset was insidious.

Postoperative Onset The greatest number of subphrenic abscesses occur postoperatively or as a result of an intra-abdominal lesion which should have been treated surgically before the process had spread to the subphrenic area. Not infrequently, the subphrenic area is involved at the time of surgical intervention but this is not recognized clinically. In other instances it is the result of contamination at the time of operation. If after an abdominal operation for a suppurative process the postoperative course is not smooth, even if weeks have elapsed, if no other satisfactory explanation can be given for the unusual course, a subphrenic infection should be considered until it is ruled out. In the present series there were 69 (49 per cent) which belonged to this group.

Recurrent Onset In these cases the patient usually gives a history of an ill-defined infection following either an abdominal accident, a surgical operation or infection elsewhere in the body. The history often suggests a subacute hepatitis with recurrent acute exacerbations. At the onset of a recurrent 'flare-up' there is vague upper abdominal or costovertebral pain, anorexia, diaphoresis, fever which may become irregularly elevated, and perhaps frequent chills. As the process becomes more acute, the symptoms become more pronounced. Between such episodes the patient feels malaise, is fatigued and becomes weaker as the condition progresses. Any other complications which may ensue during the illness will produce additional symptoms. In the present series of cases there were seven (5 per cent) of the cases which presented symptoms of recurrent infection of the subphrenic area.

In practically all cases of subphrenic abscess the mode of onset is essentially the same, the only differences being (1) the acuity of the clinical course and (2) the altered train of symptoms caused by differences in the location of the abscess. Clinically, it is often impossible to localize the site of a subphrenic abscess more precisely than to say that it is on the right or left side, above or below the liver. It was essentially for this reason that Piquand⁷ classified subphrenic abscesses as (1) *infrahepatic*, presenting signs of abdominal involvement, (2) *suprahepatic*, presenting signs of thoracic involvement and (3) *retroperitoneal*, presenting signs of lumbar involvement. More recently Mitchell⁸ has again called attention to the fact that a strict anatomic classification, such as presented above, is not always serviceable clinically. This is particularly true in those instances in which the infection involves more than one anatomic subdivision of the subphrenic area. In such latter instances, the clinical manifestations will vary according to the location of the abscess, its size, the acuteness of its onset, and the nature of the bacterial flora within the abscess.

DIAGNOSIS

Brown⁹ aptly states that the chief reason for not recognizing this condition is the failure to consider the possibility of its existence. In any case of persistent elevation in temperature of unexplained origin and a history of sepsis, a subphrenic abscess should be considered in the differential diagnosis. In the early or subacute case the onset is usually indefinite, with minimal symptoms, such as malaise, fatigue, poor appetite, pallor, vague pains at the site of the abscess and a low grade fever. As the condition progresses, the temperature and pulse become elevated and tend to assume a septic course. The patient may also become prostrate, have chills, and perspire profusely. Nausea and, in the more acute cases, vomiting have set in before this stage if the lesion is intraperitoneal. At a still more advanced stage the patient has anorexia, loss of weight, pain in the shoulder and neck corresponding to the side of the lesion, some respiratory distress, short spasmodic bouts of cough, and occasionally hiccough, belching or both. Not infrequently jaundice and anemia develop. The white blood count rises to about 20,000 with 85 per cent polymorphonuclear leukocytes. In the more acute cases the clinical course is more rapidly progressive and the symptom complex is more severe. In some of the more acute cases reported in this communication the white blood count was over 40,000 with 90 per cent polymorphonuclear cells. On examination of the patient one generally notes an acutely sick individual with a hectic flush, a warm moist skin and an anxious expression, breathing rapidly with restricted respiratory excursions of the chest on the side corresponding to the abscess. Usually the patient tends to favor the affected side by lying on it. Not infrequently the respiratory movements of the abdominal wall are restricted too. In addition a tumor mass may be visible below the costal margin in the abdomen, or bulging edematous intercostal spaces, or a mass in the costovertebral region. If it is possible, the patient should be examined in the erect and prone positions.

Subphrenic abscesses are characterized clinically by a combination of abdominal, thoracic and costovertebral or lumbar manifestations either one of which may predominate and at times mask the other symptoms.

Abdominal Manifestations Since most subphrenic abscesses are secondary to an intraperitoneal suppurative process, one usually looks first to the abdomen for the cause of a patient's failure to improve. Examination of the abdomen shows either restricted or absent respiratory movements of the upper abdominal wall on the affected side. Broadbent¹⁰ noted that under such conditions "the upper abdomen does not move with respiration on the side affected while it still usually moves on the other side, giving the curious effect of a slight bulge on the sound side in inspiration." At times there is a visible mass in the epigastric region, the skin over which may be edematous and discolored. In those instances in which subphrenic abscess follows surgical intervention for an acute gall-bladder infection, edema and

discoloration of the skin seem to be more common and more pronounced than in the other instances. This region is usually tender to touch and early presents a doughy resistance. On palpation, the rectus abdominis muscle on that side is found to be spastic and tender, beneath which there is an indefinite, tender, fixed mass, whereas the muscles on the contralateral side and in the lower part of the abdomen are less resistant. In those instances in which the abscess is suprahepatic, the liver is generally displaced downward. The lower edge of the liver may be either sharp or rounded, depending upon the extent of the accompanying hepatitis. On percussion, the area of liver dullness is enlarged downward, and if the abscess contains gas, there may be noted four zones of altered percussion note. From above downwards they are (a) a zone of normal resonance or hyperresonance of the lung substance, (b) a zone of pleural effusion or compression of the lung with dullness, (c) a zone of resonance or tympany due to gas, and (d) a zone of absolute dullness due to the abscess itself. Carter,¹¹ in reporting on left subphrenic abscess, states "The diagnosis by physical examination of an abscess beneath the left leaf of the diaphragm is even more difficult than it is when the abscess lies beneath the right half of the diaphragm, for such an abscess gives fewer physical signs of its presence. On the right, the firm large right lobe of the liver forms the floor of the abscess, whereas on the left there is little liver substance, but the abscess is encompassed below by more yielding structures, such as stomach, falciform ligament, colon, spleen and transverse mesocolon. Consequently, on the left there is apt to be less bulging in the lower thorax and costal margin, less restriction of movement of the lower portion of the thoracic cage, less local pain because of less tension of the pus and less elevation and fixation of the diaphragm itself. It is true, however, that in the case of the left anterior intraperitoneal abscess, tenderness on pressure beneath the costal margin can be elicited earlier and more definitely than on the right. If the whole space is filled with pus, one can outline a characteristic triangular mass described by Barnard as extending from under the left costal margin to a line from umbilicus to costal margin and from ensiform cartilage to umbilicus." Wahby reports the presence of gas in 32 out of 59 (54 per cent) of the cases seen at the St. George Hospital, whereas Berman¹² noted it in only 15 per cent of his cases. In the present series, 30 per cent of the cases were recognized as having gas-containing abscesses. In the entire 139 cases there were 78 (56 per cent) in which the onset of the subphrenic abscess was accompanied by abdominal symptoms.

Thoracic Manifestations The impaired respiratory movement seen in the upper part of the abdomen is also in evidence at the base of the involved hemithorax. In addition there is noted a widening of the intercostal spaces of the lower part of the chest and flaring of the lower costal structures. In those instances in which the abscess is deeply placed, there may be retraction of the intercostal spaces rather than widening and edema of the lower chest wall. The costal arch is usually tender and the musculature quite spastic in

the region overlying the site of infection. Diaphragmatic pleural pain and irritation may cause a short spasmodic cough and an increase in the respiratory rate. If the abscess is located in the anterior infrahepatic area, there is tenderness along the tenth rib anteriorly. In those cases in which the right posterior suprahepatic area is involved the tenderness is along the eleventh and twelfth ribs posteriorly. On percussion of the chest, there is elicited impairment over the lower part of the thorax and elevation of the diaphragm. In addition, there is an absence of diaphragmatic descent during inspiration and of elevation of the diaphragm during expiration. Margulis¹³ has pointed out that percussion of the affected area or costal arch is frequently accompanied by local pain resulting from the transmission of the stimulus to the pathological focus. The breath sounds in the area of altered percussion note are distant or entirely absent. Since impairment of mobility or elevation of the diaphragm will have its greatest effect upon the lower lobe, and since this lobe is situated for the most part posteriorly, the earliest pulmonary physical signs will be noted at the base of the thorax posteriorly on the side corresponding to the location of the abscess. Occasionally, with partial compression of the lung, one hears transmitted bronchial breathing in the upper area of the impaired percussion. This may extend a variable distance upwards toward the apex of the lung. In those cases in which the abscess contains gas, signs suggesting a tension pneumothorax, succussion sounds and shifting dullness may be elicited. Not infrequently a friction rub may be heard at the base of the thorax. This is due to the rubbing of the diaphragm against the inflamed upper surface of the liver. If the abscess is on the left side, the heart may be pushed upwards or rotated to the right but is not remarkably displaced to the right. In these cases one hears occasionally a clicking quality to the second heart sound in the region of the apex. Da Costa¹⁴ has pointed out that in empyema the upper limit of the fluid is concave, whereas in subphrenic abscess it is convex. The onset of 51 (37 per cent) of the present series of 139 cases was characterized by symptoms referable to the thorax.

Lumbar Manifestations Quite commonly there is a mass in this region extending outwards from below the costal margin posteriorly. The area is usually edematous, tender, and tense, and fluctuates deeply. At times the mass may be so large that it reaches the axillary region. It is dull to percussion except in those instances in which gas is present, in which case it may be hyperresonant. Pressure on the mass will cause pain locally and at times referred to the shoulder, epigastrium or anterior infrahepatic region on that side. Bogart¹⁵ has called attention to the fact that spasm of the quadratus lumborum on the affected side is commonly encountered in subphrenic abscess, resulting in scoliosis of the lumbar area. Scoliosis may further be elicited early in the course of the illness by noting the patient's inability to bend the spine from side to side, especially will this be noted when bending to the opposite side. It will also be observed that bending to the side of the abscess causes little or no pain, whereas bending toward the

opposite side is accompanied by pain. The onset of 41 (30 per cent) of the cases presented in this study was characterized by symptoms referable to the lumbar region.

ROENTGENOGRAPHIC STUDIES

Roentgenographic examinations are indispensable for the early recognition of this condition. On fluoroscopic examination of the early case, the diaphragm is found to be elevated and flattened at its dome. Quite frequently the diaphragm is eventrated into the thoracic cavity and presents an acute upper convexity. This position and form remain more or less the same during inspiration and expiration. More frequently, however (in the early case) the elevation of the diaphragm is scarcely noticeable. However,

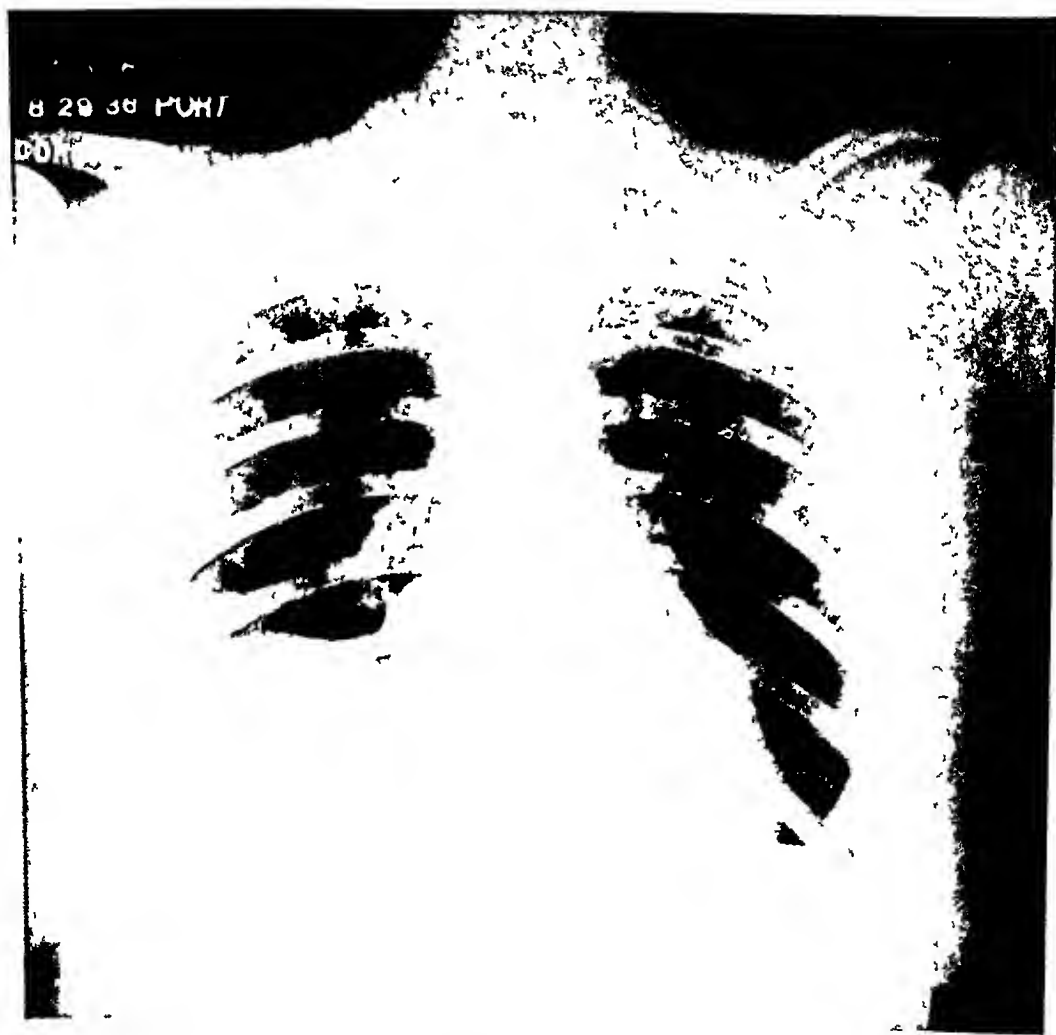


FIG. 2. Right subphrenic abscess.

There is an elevation of the right diaphragm so that its dome reaches the level of the fourth rib anteriorly. The right costophrenic angle is somewhat clouded—suggestive of fluid in the area. The cardiophrenic angle on the right side is very distinct. Also note that the heart is not displaced.

This roentgenogram is a bedside study taken in the dorsal prone position.

fluoroscopic examination of the patient in the erect position will reveal limited respiratory motion of the diaphragm. Dexter¹⁶ believes that the loss of diaphragmatic motion is almost pathognomonic of this condition. He also states that other conditions below the diaphragm will limit the motion of the diaphragm but will not completely inhibit its motion. Not infrequently a variable amount of fluid may be noted in the pleural cavity on the affected side. Underneath the diaphragm and above the liver there is a dense shadow of more or less uniform opacity or a gas bubble below the diaphragm and a collection of fluid inferior to the gas shadow. This fluid level readily changes its location as the patient's position is altered.

LeWald,¹⁷ Pancoast,¹⁸ McNamee,¹⁹ Granger,²⁰ and Sante²¹ have shown that by far the greatest single aid in the diagnosis of subphrenic abscess is a series of well taken roentgenograms. The roentgenograms of the chest should be taken in all directions, erect, prone and in the Trendelenberg position, and during inspiration and expiration. Not infrequently the patient is



FIG 3 Left subphrenic abscess

There is an elevation of the left diaphragm so that its dome is higher than the one on the right. The left costophrenic angle is not very distinct. Note that the heart is not displaced. (Same case as figure 4)

Roentgenogram taken in the erect position during inspiration

too sick to allow as much manipulation as is required in such roentgenographic investigation and, therefore, a limited number of bedside studies will have to be relied upon. In the presence of a subphrenic abscess such roentgenograms will show an elevated motionless diaphragm (figures 2 and 3), obliteration of the costophrenic angle (figures 2, 3, 4, 5 and 6), some fluid in the thorax, rotation of the heart to the opposite side and distortion of the cardiac contour (figure 4). Basilar pneumonitis may also be seen in such cases. In the later stages there is a general retraction and opacity of the

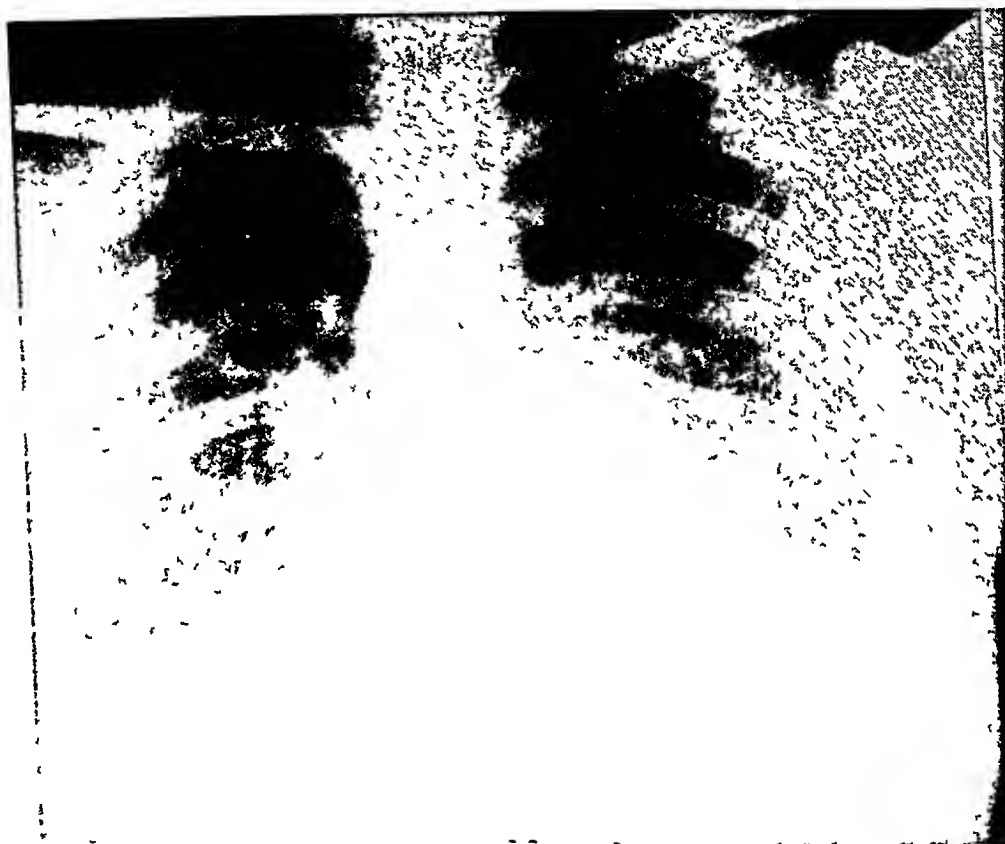


FIG 4 Left subphrenic abscess

Same case as figure 3. Roentgenogram taken in the same position as figure 3, three days later. There is further elevation of the left diaphragm. Note the distortion and rotation of the heart.

affected side (figure 11). Most of these thoracic signs are best elicited when the roentgenograms are taken in inspiration, i.e., when the contralateral diaphragm descends and that lung becomes aerated. Underneath the diaphragm on the affected side there is often seen a dense shadow or a gas bubble with a distinct fluid level below (figures 7 and 8). In the advanced case the subdiaphragmatic opacity may extend well below the liver as a homogeneous shadow. Frequently only a few of these findings will be present, they are sufficient, however, to make one highly suspicious of a subphrenic collection of pus. In such instances the diagnosis may be further facilitated by a pneumoperitoneum (Lilienthal²²). Recently Sante²¹

has again shown that this procedure may help localize the site of a subdiaphragmatic abscess and differentiate it from supradiaphragmatic conditions. It should also be pointed out that the mere presence of gas under the diaphragm does not warrant the diagnosis of subphrenic abscess. Frequently such a state is encountered in patients who were subjected to an abdominal exploration with an uneventful postoperative course,²³ or in individuals who have sustained a ruptured viscus without developing such an abscess,²⁴ and in individuals who have an hepatodiaphragmatic interposition of the colon.²⁵



FIG 5 Left subphrenic abscess

There is a gas bubble and a fluid level below the left diaphragm (extragastric?). Above the left diaphragm there is a basilar haze due to fluid. The diaphragm cannot be visualized.

Roentgenogram taken in the erect position

Roentgenographic studies of the lumbar spine and the surrounding area are often of additional aid in the early recognition of such infections. The most frequent finding is obliteration (partial or complete) of the psoas muscle shadow on the affected side (figures 9 and 10). There may also be noted a scoliosis of the spine with the concavity toward the side of the abscess and an approximation of the lower ribs and iliac crest on that side (figure 9). The liver and kidney may be depressed and the liver edge may

lose its sharp contour (figure 10) In left-sided cases, in addition to the findings noted above, roentgenograms taken in the erect position show a downward displacement of the stomach bubble with an opacity between it and the cusp of the diaphragm (figure 11) If doubt should still exist as to whether the gas is within the stomach or above it, the diagnosis may be further facilitated by filling the stomach with a radiopaque substance and



FIG 6 Left subphrenic abscess

Same case as figure 5, taken at the same time as figure 5 The left diaphragm is elevated There is also present a small amount of fluid in the left costophrenic area The elongated opacity anterior to the dorsal vertebrae is due to radiopaque material within the esophagus

Roentgenogram taken in the erect left oblique projection

then taking roentgenograms of the diaphragmatic region It will be noted that if the gas is within the stomach, it is confined to an area which assumes the contour of the stomach itself If the gas is outside of the stomach, it will cross the limits of the stomach wall as outlined by the radiopaque material, and will not, therefore, conform to the shape of the stomach This can best be elicited by taking the roentgenograms in the

erect, Trendelenberg and prone positions, in the anteroposterior, oblique and lateral projections

An early subphrenic abscess produces an ill defined clinical picture which, with the past history and roentgenographic studies, should not be difficult to recognize. That the diagnosis will be overlooked if it is not kept in mind is shown by Overholt's²⁶ case in which the diagnosis was not made until six



FIG 7 Right subphrenic abscess

The right diaphragm is slightly elevated. Underneath it there is a gas bubble (Same case as figure 8)

Roentgenogram taken in the ventral erect projection

months had elapsed, and by Lockwood's²⁷ case, in which the diagnosis was not made until 20 months had elapsed. In the cases presented in this communication the average length of time from the onset of symptoms to the time of diagnosis was four months*.

Aspiration has frequently been recommended as a diagnostic adjuvant. In the few cases of this series in which it was employed it was not of much

* This high figure is due to the fact that in three cases two years, two years and seven years had elapsed before the diagnosis was made. Excluding these cases, the diagnosis was made usually within one month after the onset of symptoms. In those instances in which it was a postoperative complication during the patient's hospital stay, the diagnosis was made within one week after the first symptoms or onset of an abnormal postoperative course became manifest.

aid In fact, in the three cases in which it would have given valuable information no pus was obtained, although surgical intervention soon after the aspiration revealed pus Like many others, the writer believes that this procedure is not entirely innocuous and should only be done immediately prior to operation so as to help locate the abscess If the needle fails to locate the pus and the clinical impression is that of a subphrenic abscess, surgical exploration should be undertaken nevertheless Weir,²⁸ as early as 1892, stated "Negative results often suggest surgical delay, and its chance

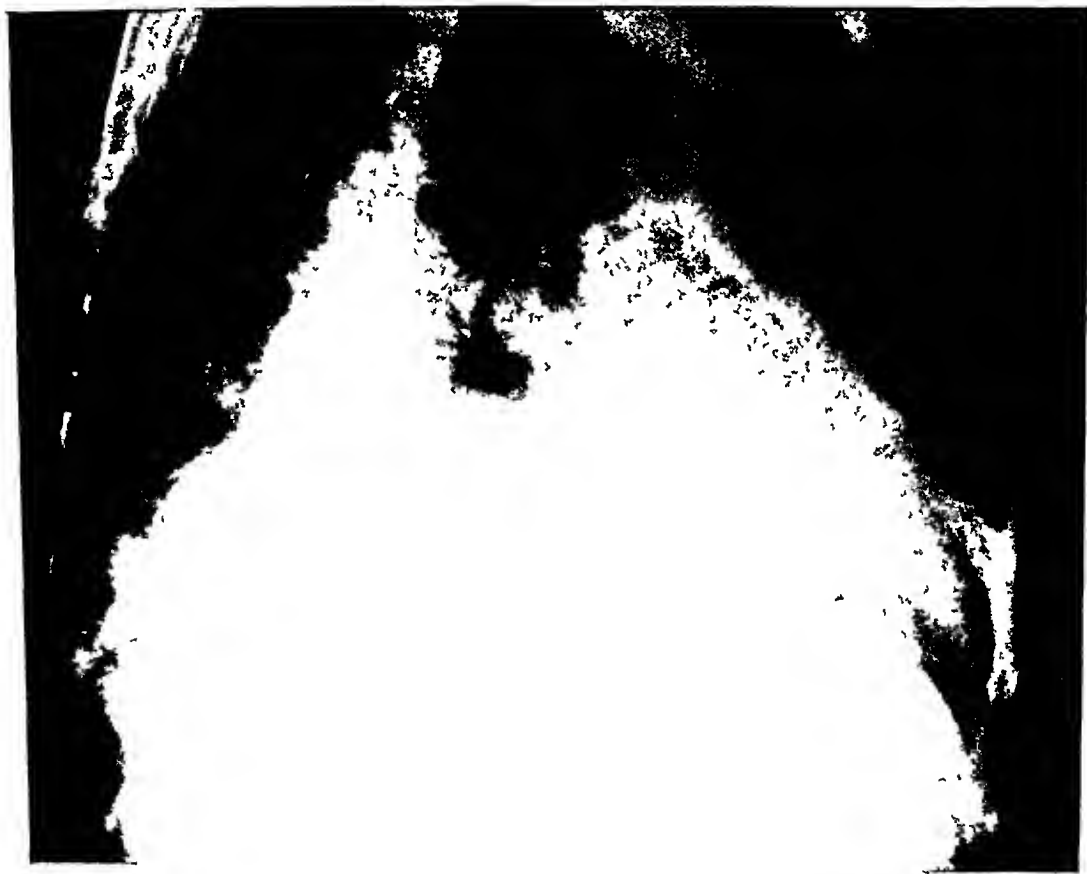


FIG 8 Right subphrenic abscess

Same case as figure 7 Roentgenogram taken the same time as figure 7 Note the two distinct fluid levels The gas bubble and fluid level to the reader's left is beneath the right diaphragm The other pair of shadows are gastric

Roentrenogram taken in the erect right oblique projection

of help in cases where help is needed as in small collections of pus, and where other symptoms are sufficiently present to determine a course of action, is a very slight one' Overholt and Donchess²⁹ condemn aspiration and report seven negative aspirations in 21 cases of proved subphrenic abscess Ochsner,³⁰ citing Hirsch's case, stated that 24 attempts at aspiration were made before pus was obtained This large number of punctures at the same site makes one wonder whether there was not some possibility of introducing infection from without Doidge and Warner,³¹ in opposing indiscriminate

diagnostic puncture of the subdiaphragmatic area, state "the presence of subphrenic abscess which was not found by diagnostic aspiration and the possible production of an empyema of the pleural cavity show the unreliability and danger of this method of examination. In our opinion, it should



FIG 9 Right subphrenic abscess

Roentgenographic study of the lumbar area. There are two radiopaque catheters in the ureters. There is a scoliosis of the lumbar spine with its concavity toward the right. The right psoas muscle is obliterated. Note that the tip of the right twelfth rib is closer to the brim of the pelvis than the one on the left.

never be used with one possible exception, that is, in an extremely ill patient where an incorrect diagnosis of subphrenic abscess with a resulting unnecessary operation might be fatal." Barnard⁶ reported a case of transpleural aspiration of an abscess, with death from collapse in three hours. If aspira-

tion fails to reveal pus, it certainly does not rule out the presence of a purulent collection. In fact, one may be more in a quandary as to the diagnosis after a negative tap than before the aspiration was instituted. Certainly such a state of mind will lead to procrastination and further complications. At best, it would be advisable to disregard a dry tap.



FIG 10 Right subphrenic abscess

The lumbar vertebrae are in a straight line. The tip of the right twelfth rib is at the same level as the left. The upper part of the right psoas is indistinct. The liver is depressed and its edge rounded. The right kidney is pushed down so that its lower pole is within the brim of the pelvis.

COMPLICATIONS

Although this condition is rarely primary and is in itself a complication, because of the nature of the process and the devastating effects of its se-

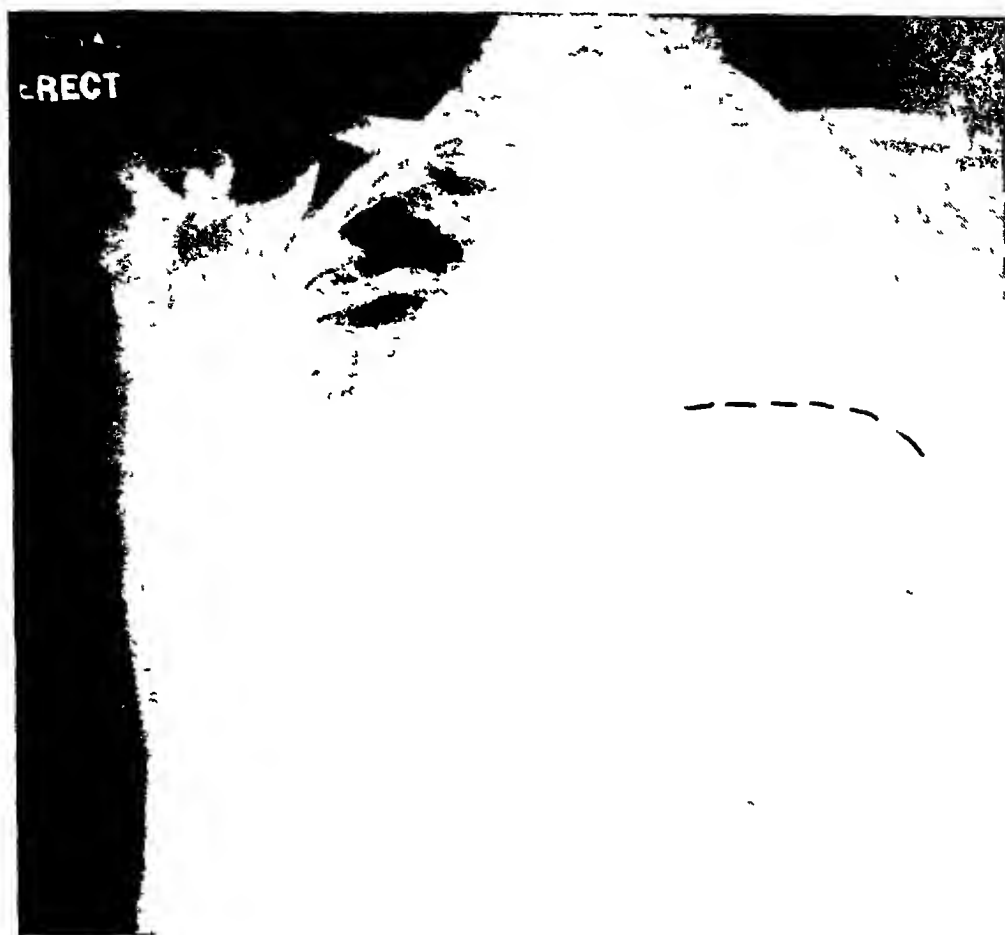


FIG 11 Left subphrenic abscess

There is a general opacity of the left hemithorax. Diaphragm could not be seen on the roentgenogram. (The dotted line indicates the level of the diaphragm as seen on a later roentgenographic study.) Beneath the diaphragm there is a large extragastric gas bubble and a fluid level.

Roentgenogram taken in the dorsal erect position.

quelaes, one may consider it a primary process and its sequelae as complications. Complications following subphrenic abscess will depend on (1) the acuteness of the onset and the rapidity of spread of the infection producing the abscess, (2) individual resistance to that infective organism, (3) the degree of peritoneal soiling on removal or drainage of the etiologic process, (4) the duration of the subphrenic abscess before its recognition, and (5) the adequacy of surgical care of the subphrenic abscess.

The complications of subphrenic abscess are as follows:

(A) *Systemic Complications* These consist of (1) sepsis, (2) prostration, (3) anemia and finally (4) cachexia.

(B) *Abdominal Complications* These consist of (1) local enlargement of the abscess producing pressure upon the surrounding structure and impairment of function, (2) rupture of the abscess into the extraperitoneal space producing a spreading retroperitoneal infection, (3) rupture of the

abscess through the surgical wound or through the skin, (4) rupture of the abscess into the peritoneal cavity, thereby producing peritonitis, and (5) rupture of the abscess into one of the hollow viscera

In the cases reported in this communication it was frequently impossible to tell whether a so-called complication was a sequel to the abscess or was coexistent with the subphrenic abscess at the time of the diagnosis of the latter or whether the cause of the subphrenic abscess was the same as that of the other abdominal complications. It seems as though many of the abdominal complications frequently noted in cases of subphrenic abscess are associated complications rather than caused by it

(C) *Thoracic Complications* These consist of (1) pleural effusion, (2) empyema, (3) bronchopleural fistula, (4) abscess of the lung, (5) pneumonia or pneumonitis, (6) pericarditis, (7) mediastinal abscess or mediastinitis, (8) pneumothorax or pyopneumothorax, (9) perforation of the diaphragm, and (10) pulmonary embolism

1 Pleural effusion is variously estimated as being present in from 9 to 100 per cent of the cases. This complication was noted in 36 (25.9 per cent) of the cases presented in this study

2 Empyema may develop as a sequel to a serous pleural effusion or as a direct infection of the pleural space. Organisms may enter the pleural cavity either through the lymphatics from below the diaphragm or by rupture of a subphrenic abscess into the pleural space, or secondary to a pneumonia or lung abscess in a patient who also has a subphrenic abscess. Empyema associated with subphrenic abscess has been variously estimated as occurring in 11.9 to 42.5 per cent of the cases. In this series it was noted in 18 (12.9 per cent) of the cases

3 Bronchopleural fistula is usually secondary to a pneumonia, lung abscess or empyema. There is no record of a case in which a preceding infection such as those mentioned above was not present or did not antedate the development of the fistula. Bronchopleural fistula secondary to subphrenic abscess and its sequelae has been variously estimated to occur in from 5 to 20 per cent of the cases. It was a complication in five (3.6 per cent) of the cases in the present series

4 Abscess of the lung is usually the result of a lymphatic extension into the lung, a postpneumonic complication, or embolic in origin. Abscess of the lung following a subphrenic abscess has been variously estimated as occurring in from 6 to 16 per cent of the cases. In the present series it was noted in 10 (7.2 per cent) of the cases

5 Pneumonia or pneumonitis is either a superimposed infection or an extension of the process from below the diaphragm into the lung. The incidence of pneumonitis following subphrenic abscess has been variously reported as being from 5.9 to 33.3 per cent. It was found in 11 (7.9 per cent) of the cases in the present series

6 Pericarditis is usually the result of a lymphatic extension of the infection from below the diaphragm, especially on the left side, or from an

empyema thoracis, pneumonitis or abscess of the lung The incidence of pericarditis following subphrenic abscess has been variously reported as being from 6 to 20 per cent It was encountered in but three (2.1 per cent) of the cases reported in this paper

7 Mediastinitis or mediastinal abscess may result from a direct extension of the infection along the outside of the pleura and between the mediastinal blades of the parietal pleural reflection, or as a direct extension into the mediastinum from a subdiaphragmatic abscess, or from pneumonitis which in turn is due to a subdiaphragmatic infection The incidence of mediastinitis or mediastinal abscess following subphrenic abscess has been variously reported as being from 2.9 to 7 per cent In the present series it was seen in one (0.7 per cent) of the cases

8 Pneumothorax or pyopneumothorax may be the result of a spontaneous rupture of the lung due to any of its causes, or to infection of the pleural space by a gas-producing organism, or to a sinus tract extending from below the diaphragm to the pleural space The incidence of pneumothorax or pyopneumothorax following infections of the subphrenic area has been variously reported as being from 10 to 30 per cent In the present series of cases it was encountered in nine (6.5 per cent) of the cases

9 Perforation of the diaphragm may be the result of a pathologic process above or below the diaphragm The incidence of diaphragmatic perforation following subphrenic abscess has been reported as being from 5 to 49 per cent It was seen in eight (5.7 per cent) of the cases in the present series

10 Pulmonary embolism may arise from the original pathological process, from the subphrenic abscess, or from an associated pulmonary infection There was but one instance (0.7 per cent) of pulmonary embolism in this series

General Thoracic Complications In the cases under review there were a number of instances in which symptoms referable to the chest were among the earliest manifestations of an illness which later proved to be a complication of subphrenic abscess In the 139 cases there were 78 cases with 102 thoracic complications There were 58 cases with one intrathoracic complication, 16 with two intrathoracic complications, and four with three co-existing intrathoracic complications Supradiaphragmatic complications were usually found to be due to the following causes (1) neglect or oversight of the primary cause, (2) failure to make an early diagnosis of subphrenic abscess, (3) inadequate surgical care for the subphrenic abscess in spite of an early diagnosis, (4) very rapid spread of the subdiaphragmatic infection, and (5) the patient's failure to present himself to the physician until complications are present

PROGNOSIS AND MORTALITY

In all cases of subphrenic abscess the prognosis should be guarded, particularly so when associated with a pathological process elsewhere which is not

well under control. The prognosis is more favorable in those cases in which the diagnosis is made early, in which adequate drainage has been established, and in which there is freedom from intrathoracic or other associated complications. Conversely, the prognosis becomes poorer when the diagnosis is not made until late, when the drainage of the abscess is inadequate and when there are intrathoracic complications. Delay in the institution of what would otherwise have been adequate therapy will often produce poor results. The mortality is greatest in those cases in which pulmonary complications develop. In the presence of intrathoracic complications the mortality in the group of cases presented in this study was 35 per cent, a total of 27 deaths. Beye,³² in a review of the thoracic complications in subphrenic infections, reported a mortality of 43.5 per cent.

Taking all cases of subphrenic abscess together, the mortality has been estimated to be 100 per cent in those instances in which surgical drainage was not instituted (Deaver), and 38 per cent in those instances in which operation was performed (Gatewood). More recently, with the newer concepts of the management of such cases, the mortality has declined to about 25 per cent. Even this mortality is too high. It is hoped that by earlier recognition of this condition therapy will be instituted earlier and mortality will be reduced still further.

SUMMARY AND CONCLUSIONS

A general résumé of the subject of subphrenic abscess has been presented. It has been pointed out that the diagnosis of this condition is not difficult if one keeps it in mind. Early recognition of this condition requires (1) knowledge of the course of the preceding illness, (2) a carefully conducted physical examination, and (3) a series of well taken roentgenograms.

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RESPIRATION AS A FACTOR IN THE CIRCULATION OF THE BLOOD *

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THE belief that respiration assists the return of blood to the heart is not new, but there is a lack of consensus among physiologists as to the mechanism of this cardiorespiratory function. Many believe that abdominal and pulmonary venous blood is aspirated to the heart. It is the purpose of this paper to discuss the respiratory act as a propulsive mechanism in the circulation of the blood.

PHYSIOLOGIC DATA

The right ventricular output of blood per minute is necessarily the same as that of the left ventricle, so that the volume output of the latter may safely be utilized for our purposes. At rest the flow per minute from the left ventricle is estimated to be from five to eight liters,¹ and after strenuous exercise it may rise to 30 to 40 liters. These figures indicate that at rest, with a respiratory rate of 20 per minute, the lungs return to the heart between 250 and 400 c c of blood per respiratory cycle.

The volume of blood present in the lungs varies with the phase of respiration. Starling² states the amounts to be normally, inspiration $\frac{1}{12}$, expiration $\frac{1}{15}$ to $\frac{1}{18}$, with a possible increase to as much as $\frac{1}{6}$ or more of the total blood in the body. Best and Taylor³ are the authorities for the figures of normally, inspiration 9 per cent, expiration 6 per cent, and under certain circumstances an increase to 20 per cent or more. These figures indicate that, if the total blood volume in the body is 5 liters there are 83 to 139 c c less blood in the lungs during expiration than inspiration, according to Starling, and 150 c c less according to Best and Taylor.

The intrapleural pressure normally is below that of the atmosphere. It averages 3 to 5 mm Hg below during expiration and 5 to 10 mm during inspiration. This "negative" pressure at times of deep breathing may amount to 30 mm Hg.⁴ When the elasticity of the lungs is reduced it has been found⁵ that the intrapleural pressure becomes positive toward the end of expiration.

The mean pressure in the pulmonary veins is at or about zero, it is, however, somewhat greater than the mean pressure in the left auricle. It is also stated⁶ that this same venous pressure undergoes but slight increase when an increased output of the right ventricle causes a rise in the arterial side of the pulmonary circuit. In other words, the gradient of fall in pressure is steep between the pulmonary artery and the capillary field of the lungs regardless of the degree of pressure present in the pulmonary artery.

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THE RESPIRATORY CYCLE

Inspiration Thoracic phase During inspiration the capacity of the thorax increases, and there is a reduction of the intrapleural pressure to 10 or more mm Hg below atmospheric pressure. The lungs follow the chest wall closely as they are distended by the incoming air under atmospheric pressure. The capillaries and veins, both of which are thin-walled, tend to dilate and can contain a greater amount of blood. This dilating effect is said⁶ to operate likewise during diastole on the cardiac auricles which are thin-walled and subject to essentially the same intrathoracic pressure changes as are the lungs.

Abdominal phase During inspiration the contracting diaphragm descends, thus enlarging the thoracic cavity downward and contributing to the lowering of pressure inside the thorax. This descent of the diaphragm at the same time raises the intra-abdominal pressure⁷ to a degree somewhat dependent upon the tonus of the musculature of the abdominal wall and supplies a positive force which, acting on thin-walled capillaries and veins, presses their content of blood onward into the vena cava and thence into the thorax and right auricle.

Expiration Thoracic phase With the beginning of expiration the lungs shrink in size owing to the action of the elastic tissue they contain. The thoracic wall shrinks largely because of the elastic reaction of the stretched costal cartilages. The intrapleural pressure rises. There is some evidence⁸ that the bronchial muscles contract with each expiration and increase the elastic recoil of the lungs. There is also a delicate system⁹ of muscle fibers, quite apart from those of the bronchial muscles, whose function is uncertain, but it is believed that they may contribute to the lessening in the lung volume⁹.

Abdominal phase The relaxed diaphragm moves upward, thus aiding in the pressure exerted on the lungs. It is stated¹⁰ that an increase in the tone of the abdominal musculature during expiration brings about a rise in the abdominal pressure, with the result that the relaxed diaphragm is pushed up into the thoracic cavity. It is improbable, however, that the intra-abdominal pressure is as high during expiration as it is during the inspiratory contraction of the diaphragm. The diaphragm is well compared to a piston and the thoracic cavity to a bellows.

Return of Blood to the Left Auricle The evidence presented supports the view that respiration provides a mechanism by which venous blood is pressed onward into the vena cava and right heart. It is clear enough that the contractions of the right ventricle then drive this blood onward into the pulmonary field. The next problem is what makes the blood move from the lungs to the left auricle.

The statistics cited regarding the amount of blood flowing per minute through the lungs indicate that the flow is rapid and subject to great increase at times of physiologic need. The difference in blood content of the lungs

during inspiration and expiration may be due to a greater volume intake of blood during inspiration or a greater output during expiration, or both. In favor of the former is the effect of inspiration in accelerating the venous return to the right heart, which in turn propels it into the pulmonary artery. Then the lowered intrapleural pressure that occurs during inspiration permits the smaller vessels of the lungs to dilate more readily and provide a greater capacity for blood.

What becomes of this excess of blood in the pulmonary circuit? Does it merely flow off at a steady rate to the left auricle or is it squeezed out of the pulmonary capillaries and veins by the increase of intrapleural pressure that is a feature of the expiratory phase of respiration? If the process by which the pulmonary capillaries and veins are able to dilate during inspiration and accommodate a larger amount of blood is to continue, then there must be some mechanism during expiration by which they become smaller and are relieved of the extra content of blood. Expiration is known to expel air from the lungs. Does it not also expel blood?

Physiologic literature does not disclose a general agreement regarding the mechanism which brings about the return of blood from the lungs to the heart, at times the matter remains unmentioned. The statements are similar to those expressed regarding the return of venous blood from the abdominal veins to the right auricle. In brief, the blood is either aspirated by the left auricle or flows as a result of a positive pressure.

The process of aspiration seems not applicable here, since aspiration can not be successful when it must operate through thin-walled and collapsible tubes, which is the character of the pulmonary veins. How efficient is a straw as a drinking tube when the straw has lost its rigidity? If the left auricle aspirates the blood from the pulmonary veins this mechanism must needs be efficient when, in response to stress, there is a greatly increased flow of blood through the lungs.

It is stated ¹¹ that during diastole both intra-auricular and intra-ventricular pressures are below atmospheric pressure, and that this is not owing to any sucking action of the heart but to the transmission of the negative pressure in the thorax through the slack heart wall. Today there are probably few, if any, who believe that the ventricle *sucks* blood from the adjacent auricle, and how can it if the negative pressure be due to the effect of the negative intrathoracic pressure which operates on both cardiac chambers and perhaps more on the thinner walled auricle? Similarly, how can the left auricle aspirate from the pulmonary veins?

The conception that the aspirating power of the auricle is acquired by transmission of the negative intrathoracic pressure makes one conjecture what happens to the outflow into the left auricle during expiration, when intrapleural pressure is less negative and may even be positive. Auricular systole is brief and should hinder but momentarily the entry of blood from the pulmonary veins, but the expiratory phase of respiration is distinctly longer than the inspiratory and might well, because of the higher intra-

pleural pressure associated with it, seriously interfere with inspiration by the auricle, if that be the method by which it obtains its content of blood. The dilemma would become greater at times of stress, when the blood flowing from the pulmonary circuit into the left auricle is markedly increased, since then the more vigorous expiration tends to raise the intrapleural pressure to levels in excess of that of the atmosphere. In other words, the aspiration mechanism would be required to be more efficient when the conditions on which it is based are less favorable or even non-existent.

It is known that the onflow of blood into the left auricle is continuous, save perhaps during the brief period in which the auricle is in systole. Because of the fact that the expiratory phase of respiration is longer than that of inspiration and that the intrapleural pressure levels during expiration may be unfavorable to aspiration by the heart it would be a more efficient mechanism if the onflow of blood were dependent upon the expulsive action of respiration rather than that of the heart. It seems probable that just as the lungs expel air so they do blood, a view which is supported by Best and Taylor.¹²

A peculiarity of the pulmonary capillaries and veins is that their caliber is to a very large extent dependent upon the changes that occur in the intrathoracic pressure with each inspiration and expiration.¹³ These vessels become dilated during inspiration and contracted during expiration. The increase in pressure during expiration is ample to drive the blood toward the left auricle.

A recent article¹⁴ mentions the belief that during surgical manipulation of the lungs air may be sucked into the pulmonary veins and cause death by air embolism, but further points out that autopsies fail to disclose air. A textbook¹⁵ on this field of surgery mentions the occurrence of air embolism solely as a complication of the introduction of air into the chest under pressure, namely in artificial pneumothorax. Observation of a recent lobectomy discloses that if the pulmonary veins are torn they bleed and require ligation.

Regarding the correctness of the mechanism herein suggested, the question may be raised, why is not the blood driven backward in the pulmonary circuit? This question is the more pertinent since the pulmonary veins are not equipped with valves.¹⁶

The answer to the foregoing objection is obtained by consideration of the structure of the lungs and pertinent part of their vasculature. The pulmonary veins commence in the pulmonary capillaries, and coalesce into larger branches which run along the substance of the lung toward the hilum of the organ. The lung during the contracting phase shrinks in toward the hilum and hence it is toward this part that the blood would be pressed. The caliber of the veins grows larger toward the hilum and the latter is the last part of the lung to be subjected to the expiratory rise of intrapleural pressure and the elastic recoil of the lung. An analogy is found in a water-saturated sponge which gives up the water as it is compressed from the outside by one's hand.

There is some uncertainty regarding the action of the vasomotor nerves on the pulmonary vessels, and it would appear unnecessary to consider them since the mechanical features of respiration are sufficient to drive blood onward to the heart

COMMENT

It appears that there is ground for the assertion that the respiratory act provides mechanisms which propel the blood from both venous systems to the respective side of the heart. This means that respiration is an important factor in the circulation of the blood and warrants adequate attention.

When one realizes that the pulmonary circuit is required to receive and send onward an amount of blood that varies from 5 to 8 to as much as 30 to 40 liters per minute, it becomes obvious that the maintenance of a healthy respiratory function is of great importance. One can readily call to mind a variety of conditions which may impair respiration and be followed by symptoms such as shortness of breath and dyspnea. In patients it is often difficult to determine the extent to which such symptoms are caused by malfunction of the respiratory act or of cardiac contractions. Man, in a sense, is clearly a heart-lung preparation. It is believed that too exclusive attention to the heart has caused us to overlook the respiratory factor in the circulation of the blood and maintenance of health.¹⁷

CONCLUSIONS

The respiratory act plays a significant part in the circulation of blood.

The blood from both the abdominal and pulmonary veins is propelled rather than aspirated forward.

Adequate attention to impairments in the circulatory function of respiration throws new light on a variety of clinical problems and offers opportunity for measures of prevention and treatment.

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THE RÔLE OF THE ENDOCRINES IN ANAPHYLAXIS AND ALLERGY

I. HORMONAL INFLUENCES IN ANAPHYLAXIS; A CRITICAL REVIEW

II. HORMONAL INFLUENCES IN ALLERGY, CLINICAL OBSERVATIONS *

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I HORMONAL INFLUENCES IN ANAPHYLAXIS, A CRITICAL REVIEW

It has been established beyond doubt that the endocrines influence anaphylaxis. However, the literature of this field is full of conflicting statements, and reviews have frequently added to the existing confusion by indiscriminately enumerating the opposing contentions.

Some of the discrepancies are probably due to the fact that the experiments were not carried out under comparable conditions. In many instances there are no data concerning the sex or age of the animals, factors which unquestionably play an important rôle in this type of investigation. In some instances the effects of a given hormone in male animals were examined by one group of workers, in females by another, in one group of experiments large doses were used, in others small ones. Frequently, also, conclusions have been reached on the basis of entirely insufficient experimental data. Most papers of the latter category have not been included in this review.

The rôle of the various endocrine glands in anaphylaxis has been studied by observing the effects of the application of their hormones or of the removal of the gland on anaphylactic reactivity. The most thoroughly examined endocrine in this connection is the thyroid.

I *Thyroid*

(a) *Application of thyroid extract* In guinea pigs application of smaller amounts of thyroid after established sensitization diminishes the severity of anaphylactic shock¹; larger amounts given during the sensitization period or after established sensitization enhance the anaphylactic reaction². Rabbits which were treated with thyrotropic hormone were more susceptible to shock than the controls³.

The correctness of these findings has lately been questioned by Stictzel⁴ who used as a criterion of anaphylactic reactivity the drop in temperature frequently observed in shock. Stictzel found that in guinea pigs which had been injected with thyroid extract during the sensitization period, the drop in temperature was less than in the controls.

(b) *Thyroidectomy* A considerable amount of work has been done to ascertain the influence of thyroidectomy on anaphylaxis. Most of these experiments were carried out in guinea pigs and rabbits.

In guinea pigs thyroidectomy performed nine to 31 days prior to the first sensitizing injection,⁵ or simultaneously with,⁶ or up to six days after⁷ this injection, causes a marked diminution of the severity of the anaphylactic reaction. Thyroidectomy performed 20 days after the first sensitizing injection no longer exerts an influence on the anaphylactic reaction.⁶

Thyroidectomized guinea pigs which were fed thyroid during the sensitization period reacted just as intensely to the shocking reinjection as the controls with intact thyroid.⁷

Appelmans,⁸ in a frequently quoted paper, stated that thyroidectomy did not influence anaphylactic shock in guinea pigs. The experimental data presented by him are absolutely inconclusive, and although Képinow and Lanzenberg⁹ pointed this out 17 years ago, Appelmans' contention has not been repudiated. It should finally be discarded.

More recently Spinelli, who used the Dale technic to study the effect of thyroidectomy in guinea pigs, came to the conclusion that the operation does not affect the degree of sensitization in this species. His paper is not convincing, as it is not based on quantitative experimentation.

Thyroidectomy prior to sensitization not only mitigates shock in rabbits but also alters the course of the reaction (Fleisher and Wilhelmj).⁵ In this connection Eickhoff and his collaborators³ even speak of an "inverse shock."

The diminished intensity of anaphylactic shock in thyroidectomized guinea pigs and rabbits is probably due partly to decreased antibody formation,¹⁰ partly to altered reactivity of the animals due to a lack of hormone. This latter assumption is based on the fact that thyroidectomized, sensitized rabbits and guinea pigs which received thyroid extract showed normal or even excessive anaphylactic reactivity.^{7, 8, 9, 10}

Houssay published two papers on the influence of thyroidectomy on anaphylaxis in dogs. In the first, with Sordelli,⁵ no effect was noticed, in the second, with Cisneros,¹¹ marked diminution of anaphylactic reactivity was observed. Houssay believes the findings of the second paper to be valid.

II *The Adrenals*

(a) *Application of adrenalin and cortin* It will not be necessary to discuss the thousandfold observed acute action of adrenalin in preventing anaphylactic reactions in the various species, including man.

If confirmed, the findings of Haag and Koenig¹² concerning the effect of prolonged use of adrenalin in guinea pigs should be of great significance also in human pathology. In these experiments, guinea pigs which received injections of adrenalin every other day for two weeks during the sensitization period and for two weeks thereafter were much more susceptible to shock than the controls.

Adrenal cortex extract administered to sensitized dogs¹³ and guinea

pigs¹⁴ at varying times prior to the shocking reinjection decidedly diminishes the severity of shock

(b) *Adrenalectomy* Sensitized guinea pigs which were adrenalectomized eight days prior to sensitization were found to be eight times more susceptible to fatal shock than the controls¹⁵ Passively sensitized, adrenalectomized guinea pigs showed the same degree of shock as the controls¹⁵

Although the results of these experiments are clear cut, the experiments carried out on rats are even more convincing Normal, well fed rats are exceedingly resistant to anaphylactic shock, rats adrenalectomized prior to sensitization died from shock in a large percentage of cases¹⁶ Wyman¹⁶ believes that this increased susceptibility to shock is due to lack of medullary adrenal tissue rather than to cortical insufficiency Of 15 adrenalectomized animals which had autoplasmic cortical transplants, 40 per cent died from shock, approximately the same percentage of fatalities as in the adrenalectomized rats which had no transplants

III *Pituitary*

(a) *Application of pituitary extract* The severity of anaphylactic shock was markedly diminished in young male guinea pigs which received large doses of anterior pituitary extract,¹⁷ "gonadotropic hormone,"¹⁸ and pregnancy urine extract¹⁷ prior to sensitization or during the sensitization period

Posterior pituitary extract administered during and after the sensitization period had the opposite effect¹⁹

(b) *Hypophysectomy* Male rats which were hypophysectomized when they were 65 to 75 days old and which received the shocking reinjection 47 days after operation were highly susceptible to fatal anaphylactic shock All the normal controls survived reinjection of the antigen Antibody formation, however, was essentially the same in both groups, which would indicate that the enhanced anaphylactic sensitivity was due to altered reactivity of the operated animals²⁰

IV *Follicular Hormone* The experiments concerning the influence of follicular hormone on anaphylaxis are contradictory In Schafer's²¹ experiments 47 young, adult, female guinea pigs received 10,000 to 15,000 benzoate units of Progynon-B during the sensitizing period Twenty-eight guinea pigs, or 57 per cent, died in anaphylactic shock, whereas there were only 24 fatalities or 33 per cent in the 73 controls Farmer* could not confirm these findings In his experiments, in which he followed Schafer's technique the mortality from shock was the same in the Progynon-B animals as in the controls

V *Pregnancy* There is only one acceptable paper on this question in the literature Ratnofsky²² who worked with rats, observed slight difference between the occurrence of anaphylactic shock in pregnant and non-pregnant animals In 12 pregnant sensitized rats there were two severe shocks; in

the control group of 17 non-pregnant sensitized rats four animals suffered severe reactions

Lumière and Couturier²³ state that pregnant guinea pigs are almost entirely resistant to anaphylactic shock. These authors do not state the number of animals used, nor do they give any experimental details. Their paper cannot be looked upon as conclusive.

SUMMARY AND CONCLUSIONS

1 The endocrine glands exert a distinct influence on anaphylactic reactivity

2 This influence manifests itself in enhanced or in diminished reactivity

3 The altered reactivity is due to changes (a) in antibody formation, or (b) in the sensitized animal's capacity to react to renewed contact with the sensitizing antigen

These assumptions are based on the following observations (a) Thyroidectomy prior to sensitization leads to marked inhibition of precipitin formation (in rabbits) and to diminished severity of anaphylactic shock (b) Application of thyroid extract to guinea pigs after completed sensitization enhances or diminishes the severity of anaphylactic shock depending on the amounts of thyroid administered. Application of thyroid extract to thyroidectomized sensitized rabbits and guinea pigs leads to normal or even excessive anaphylactic reactivity. Hypophysectomy (in rats) prior to sensitization leads to enhanced severity of anaphylactic shock without exerting an influence on precipitin production

4 Although the influence of the endocrines on anaphylaxis has been conclusively established, further experiments should be carried out in which stress is laid on quantitative considerations and on the sex and age of the animals

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II HORMONAL INFLUENCES IN ALLERGY, CLINICAL OBSERVATIONS

Although there are numerous references in the literature on sensitization to endocrine preparations in man, comparatively little evidence has been compiled concerning the influence of the endocrines on the course of allergic diseases. Although clinical observations clearly demonstrate this influence, they are contradictory and confusing: allergic manifestations are associated with hyperthyroidism or with hypothyroidism, they sometimes first appear at the menopause, whereas occasionally, protracted cases of allergy subside at the climacteric, in some instances an allergic condition occurs for the first time during pregnancy, whereas in others it subsides during gestation.

It is difficult, at the present time, to explain these discrepancies. In order to be in a position to do so it would be necessary on the one hand to define accurately the endocrinological situation, and on the other to show that the described disease really has an allergic basis. One will not be able to clarify the first point without the help of extensive quantitative hormone studies, and although it will frequently be less difficult to analyze the allergic angle, it will also often be a source of uncertainty. We are prone today to look upon asthma, urticaria, angioneurotic edema, etc., as "allergic" diseases, i.e., to regard them as due to hypersensitiveness. Undoubtedly they are, in a majority of cases, but there are indications that there are exceptions to this rule.¹ Furthermore, the presence of a causative allergen cannot always be demonstrated, and without this prerequisite one cannot conclusively prove the allergic origin of the condition. Under the prevailing circumstances a discussion of the literature will not be attempted, as it would not tend to clarify the situation.

In the following cases we were sometimes able to demonstrate the presence of an allergen, in other instances this was impossible. From a clinical point of view we, nevertheless, feel entitled to classify these latter cases also as "allergic."

In our experience the cases of allergic conditions which were influenced by endocrinological factors were all observed in women. Clinically they were connected with the menstrual cycle, pregnancy and the menopause. Therapeutically a number of them were benefited by the administration of hormonal preparations.

The following cases of hay-fever and asthma were distinctly influenced in their course by pregnancy.

CASE REPORTS

S. K., 34 years old, had been suffering from autumnal hay-fever since 1935. She had moderately severe nasal, ocular and bronchial symptoms. Skin tests revealed markedly positive reactions to ragweed, cocklebur and timothy pollen. The patient became pregnant in January 1938 and was delivered on October 27, 1938. During the ragweed pollinating season of 1938 she was entirely free from hay-fever symptoms. The following fall (1939) she again suffered from hay-fever. In December 1939 the patient again became pregnant and was delivered on August 5, 1940. The child was weaned after two weeks. From the beginning of September the patient had marked symptoms of hay-fever.

This patient, who had ragweed hay-fever for three consecutive seasons, had no hay-fever during the fourth season at which time she was pregnant. The following two years she again had hay-fever.

In the following case of hay-fever the influence of gestation is also very clearly visible.

A 29 year old woman developed hay-fever five years prior to examination. She had symptoms from the end of May until the middle or end of July, and from the middle of August until about the middle of October. Skin tests showed her to be sensitive to grass and ragweed pollen. She became pregnant in November 1939 and was delivered the middle of August 1940. During the grass pollinating season, during which time

she was pregnant, she was entirely free from hay-fever symptoms. However, during the ragweed pollinating period which started after her delivery she again had hay-fever.

Another woman, whom I had the opportunity of observing several years ago, had had severe bronchial asthma since early childhood. She became pregnant when she was 20 years old and was free from symptoms during the pregnancy and the lactation period. Her attacks returned shortly after the child was weaned, and she was having extremely severe asthma when I saw her seven years later.

In the above reported cases the allergic symptoms disappeared during gestation. However, we have also seen patients in whom an allergy first appeared during pregnancy. I cannot offer any explanation for these conflicting observations.

In the following instances severe angioneurotic edema and urticaria occurred shortly after pregnancy.

M. W., 26 years old, came to the Allergy Clinic on October 22, 1937. Since the beginning of October she had been suffering from severe angioneurotic edema of the lips, the eyelids, the fingers and legs. The swellings were painful and itched intensely. The patient had been delivered of her second child on July 6. She had her first menstrual period after the delivery during the last week of September. This menstruation was very profuse, painful and prolonged. The patient's past history was negative. Her sister suffers from bronchial asthma. The physical examination, the blood count, and the urine examination were normal. The patient was given ephedrine by mouth which brought temporary relief. We observed her from November until the middle of January and were impressed by the cyclic occurrence of her allergic symptoms which, we believed, were in distinct connection with her menstrual cycle. Table I illustrates these observations.

TABLE I

Menstruation	Allergic Manifestations
Last week of September	Beginning until middle of October angioneurotic edema
November 1-8 Profuse flow, painful	October 22-November 2 angioneurotic edema
December 3-8 Profuse flow, painful	November 9-14 severe angioneurotic edema December 3-11 severe angioneurotic edema
January 5-11 Profuse flow	December 16-19 severe angioneurotic edema December 28-30 severe angioneurotic edema January 3-11 severe angioneurotic edema

TABLE II

Antimitrin "S" Treatment from January 19 until March 16, 1938

Menstruation	Allergic Manifestations
February 4-8 Flow less profuse	January 23-27 mild angioneurotic edema
March 2-3	February 25 slight itching of the palms
March 5-12 (profuse flow)	March 10 and 11 itching and redness between the fingers

A gynecological examination on January 12, 1938, revealed no local condition which would have accounted for the profuse hemorrhages. The patient was given injections of 50 units Antuitrin "S" at two to three day intervals from January 19 until March 16. The total amount given was 1,540 units. The effects of this therapy on the allergic manifestations are summarized in table 2.

On April 30, 1938, the patient reported that she had had no allergic symptoms since March 11.

The following woman also developed an allergy following gestation. In her case, however, the symptoms were undoubtedly caused by hyperthyroidism.

The patient, a 37 year old woman, began suffering from very severe urticaria a few months after the birth of her third child. Her condition gradually became almost insufferable. The physical examination and extensive laboratory examinations were normal. The patient was seen by numerous specialists, including an allergist, who were not able to find an explanation for the urticaria. All instituted therapeutic measures were of no avail. Three months after onset of the urticaria clinical signs of mild hyperthyroidism were observed. Some time later the basal metabolic rate was plus 30 per cent. Although there were no other definite symptoms of hyperthyroidism, a thyroidectomy was performed at the suggestion of a well-known thyroid specialist. Almost immediately after the operation the eruptions became milder and disappeared entirely within six months. The patient has been free from symptoms for more than eight years.

We further had occasion to observe the onset of allergic manifestations at the climacteric.

E. J., 49 years old, who was referred from the Otolaryngological Clinic with the diagnosis "typical vasomotor rhinitis," was suffering from severe, prolonged paroxysms of sneezing, watery discharge from the nose, and severe pain in the nose.

This condition, which started four years previously, persisted the year round but was especially aggravated during the summer. For the preceding four to five years the patient had also been suffering from pains in various joints. These pains coincided with the nasal symptoms and improved when these improved. Concomitant with the nasal symptoms and the joint pains the patient had hot flushes and marked nervousness.

The menses began to be irregular four to five years prior to examination, for two years there had been cessation of menstruation.

The patient's personal and familial allergic history was negative. The physical examination of the circulatory, respiratory and nervous systems revealed no pathological changes. The urine examination and the blood count were normal. Skin tests showed markedly positive reactions to ragweed and cocklebur pollen and questionable reactions to house dust, horse dander, sheep wool and cotton-seed.

These sensitivities were undoubtedly acquired at the inception of the menopause.

The following patient's symptoms, which were also connected with the climacteric, were markedly alleviated by estrogenic therapy.

E. R., 48 years old, who had been suffering from vasomotor rhinitis for five years, was seen March 12, 1937.

For two months she had been having daily eruptions of severely itching urticaria which usually started on the arms or under the breast and spread over most of the body.

One week previously the patient had had a sudden attack of severe angioneurotic edema of the lips and face which lasted for 48 hours. At the same time she had an eruption of urticaria.

The physical examination and the laboratory findings were normal. Basal metabolic rate was plus 15 per cent. Skin tests were negative.

On July 12, 1937, the vasomotor rhinitis and urticaria were much milder. Urticaria occurred about once a week, the wheals were much smaller. The patient had had seven to eight recurrences of angioneurotic edema since last seen.

Between July 12 and July 26 the patient again had daily attacks of large urticarial wheals, she was also suffering more from hot flushes.

On August 2, 1937, injections of theelin (2,000 units) were started. They were given twice a week and there was soon marked improvement of the symptoms. During the latter half of August the patient received no injections and during that time the urticaria flared up. The injections were resumed toward the end of August.

On September 13, no urticaria, angioneurotic edema, nor vasomotor rhinitis was present. The patient had had itching for several days.

On November 15 there were no allergic symptoms. The twenty-first, and last, injection of theelin (1,500 units) was given.

On February 4, 1938, the patient stated that she had been well since last seen. She had had no allergic symptoms and only occasional hot flashes.

Until one week prior to August 8 the patient felt well. At that time she began to have urticaria again, and when seen on August 8 was complaining of great nervousness. She was also having hot flushes.

Estrogenic therapy had a markedly beneficial effect on the following patients whose allergic symptoms were obviously associated with their menstrual cycle. In the case of patient E. B. the question also arises whether she was entering the menopause.

E. B., a 54-year-old woman, was first seen on April 15, 1940. Shortly after the death of her mother, in February 1940, the patient started having daily eruptions of large, intensely itching urticarial wheals. The urticaria was especially severe during the menstrual period, it subsided somewhat after menstruation.

Five years previously the patient had also had urticaria. There had been no attacks in the interim.

The physical examination revealed no abnormalities. The blood count and the urine examination were normal. Skin tests for allergy were negative. The patient's menstruation was regular and profuse.

From April 19 to May 15 the patient took up to 20 tablets, or 100 units, "Torantil" daily. She was not benefited by this treatment.

From May 15 to June 12 the patient was on a diet containing no animal proteins. She showed no improvement during this time.

Theelin injections were started the middle of June. The patient received 10,000 units on June 12, 17, 21, 28. She menstruated very profusely from June 29 to July 5. On the first day of menstruation she had angioneurotic edema, and on the second and third days severe urticaria.

The theelin injections were resumed on July 8, 10,000 units were given on July 8, 12, 19. During the period from July 8 to August 2 the urticaria was much less severe and occurred less frequently.

During the menstrual period from August 2 to 7 the flow was moderately strong, there was mild urticaria. There was no more urticaria until the next menstruation from August 27 to September 1. During this period the flow was moderately strong, urticaria was very mild.

From October 1 to October 6 flow was moderately strong, there was no urticaria.

On October 16, 1940, the patient reported that she had had no urticaria.

B K, 41 years old, had had severe eczema for the preceding 10 years. Various kinds of treatment had brought little relief. There had been an exacerbation of the eczema since December 1939, and when the patient was first seen on April 10, 1940, the eruption covered almost the entire body with the exception of the face. The eczema itched severely and had caused sleeplessness. It was less severe during the menstrual period. The patient's menstruation had been irregular and painful for the last eight years.

The physical examination was negative. The blood count and the urine examination were normal. Basal metabolic rate plus 12 per cent.

It was felt that there was a connection between the patient's eczema and her menstrual disturbance. Onset of the eczema 10 years previously, irregularity of the menstruation for eight years, improvement of the patient's condition during the menstrual period. The patient was, therefore, given injections of theelin, 2,000 units were given on April 24, 29, May 8, 10, 13. There was some improvement after the third injection and less itching after the fourth injection. On May 15 and 20 the patient was given 10,000 units of theelin, her condition had improved markedly at that time. On May 22, 4,000 units were administered, and 10,000 units were given on May 29, June 5, 10, 14, 19 and 26. The patient's menstruation had become more regular, and there were only very few eczematous patches. At the end of September the patient reported that she had had no itching, no hot flushes, and no eczema in July, August and September. However, she stated that she usually felt well during July and August.

Another patient, a 37 year old woman, was first seen on August 1, 1940. She had been suffering from severe urticaria and angioneurotic edema since the end of April. From October 1939 until March 1940 she had menstruated at six to seven week intervals, since April she had been menstruating every two to three weeks. Menstrual flow was scanty.

She had received "Torantil" orally and calcium intravenously. She had been placed on various diets. Thyroid ($1\frac{1}{2}$ grains daily) had been given for several weeks during December and January as the patient's basal metabolic rate was minus 35 per cent. Ephedrine caused intensification of the urticaria, adrenalin brought no relief. Propadrine relieved the condition temporarily. The patient's condition had become markedly worse during the last week of July.

The physical examination revealed no pathological findings. The blood count and the urine examination were normal. Skin tests were negative.

It seemed obvious that in this case there also was a connection between the allergic manifestations and the endocrine disbalance.

The patient's diet was extended, however, she was not to have fruits, tomatoes, fish, sea-food, spices, or alcohol. She was given vitamin C, 150 mg, and dicalcium phosphate, 3 grams, daily. On August 7 she received 2,000 units of theelin intramuscularly. On August 8 the patient had severe urticaria which lasted until August 11. She had her menstrual period during those days. On August 13 she was given Estrone, 1,000 units, as it was thought that she might possibly not have tolerated the peanut oil in which theelin is suspended. This injection was well tolerated. On August 16, 1,400 units of Estrone were administered. On August 17 and 18 the patient again had severe urticaria. On August 26, 1,000 units Estrone were given. The following day the patient had very severe urticaria. The amount of Estrone was now markedly reduced, and on August 30 the patient received only 200 units. This injection was well tolerated. The patient menstruated from August 31 to September 3. The flow was more profuse and the patient had moderately severe urticaria. On September 6, 9, 12, 200 units Estrone were given. The patient's condition had by now improved markedly. The eruptions were much smaller and recurred less fre-

quently Three hundred units of Estrone were injected on September 16, 19, 23 and October 2 The patient menstruated from October 6 to October 10 She had very little urticaria during that period Four hundred units were given on October 10, 500 on October 14, and 600 on October 17 The patient had only occasional small urticarial eruptions, and very slight angioneurotic edema on one occasion

SUMMARY

Clinical observations are presented which demonstrate the influence of the endocrines on the course of allergic conditions No attempt is made to explain the observed phenomena

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PERIARTERITIS NODOSA; WITH REPORT OF TWO CASES *

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FOLLOWING the first descriptions of periarteritis nodosa which were published by Rokitansky, Kussmaul and Maier shortly after the middle of the last century, the disease remained, for the most part, a clinical curiosity for many years, with only occasional articles referring to it found in the literature

During the past 15 years there has been considerable interest in the subject, and as a result the literature has become much more abundant. We have come to realize that the disease, though rare, does occur frequently enough to warrant its consideration by those doing diagnostic work. Through the excellent descriptions of a considerable number of cases that have been published during the past few years it has been possible to form a fairly clear concept of the clinical manifestations of this disease. The most striking characteristic of this concept is the wide variability in the clinical aspects which may be presented by periarteritis nodosa.

Two cases are reported at this time, with a description of clinical symptoms and objective findings in which the diagnosis is sustained by autopsy in one and by muscle biopsy in the other.

CASE REPORTS

Case 1 H. B., a 39-year-old male, was admitted to the hospital on August 22, 1934. The patient stated that two years previously he had developed a chest cold. After one or two days of cough and malaise he developed paroxysmal attacks of asthma which were persistent and quite severe. He went to Tucson, Arizona, for a time, but apparently was not benefited. He took adrenalin, two to six injections per day. On October 5, 1933, he was admitted to San Fernando Hospital because of asthma and continued there about as he had been previously. The asthma tended to vary in degree of severity but never completely disappeared.

In December 1933, while home for a day or two visiting, he had a sudden onset of extreme pain and swelling in the right leg which started in the region of the ankle but gradually progressed up to the knee. There was quite severe aching pain throughout the leg. He returned to the hospital, and it was thought that he had rheumatism. He was treated accordingly, with a diagnosis of "subacute rheumatic fever." Following this he developed some palpitation of the heart and was told that he had a leakage and that his heart was irregular. After a couple of weeks the pain and swelling decreased, but the ankle remained swollen. The leg was somewhat weak, and there was slight numbness of the ankle. The patient gradually recovered and was up and around without the use of a cane. In April he again began to feel bad. There was pain and aching in the calves of his legs, and the ankles, left arm, wrist and hand became swollen. He developed a red blotchy eruption over the legs and abdomen at

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this time, which was associated with considerable fever and general malaise. There was some itching and apparently some wheals of urticarial type. He had a sore throat at this time. After two or three weeks the swelling and pain gradually went out of the limbs, but they were extremely weak and there was a definite numbness below the knees. This increased, the muscles atrophied, and the numbness became marked. There was more or less distress in the nature of aching pain.

He continued to have purpuric eruptions every two to seven weeks lasting seven to ten days. It was associated with considerable fever and malaise, also the joint and muscle pains were more severe at this time. After the appearance of purpura there were frequent urticarial wheals, and on one or two occasions the patient had swelling of the face so that he could not open his eyes. There was considerable itching. There was marked anorexia most of the time and occasionally slight indigestion. There were never any definite abdominal cramps, and there was no history of hematemesis or melena associated with the attacks.

Later the arms began to be affected by weakness, atrophy and numbness. The symptoms in the left arm were very marked, but he recovered to some degree so that he could use it.

The first blood count taken revealed that the man had an eosinophilia and also a leukocytosis which varied from 7 to 20,000 cells with from 5 to 8 per cent eosinophiles.

The asthma was about the same as it had been prior to this development. On a couple of occasions prior to the onset of the purpura there was epistaxis but no bleeding from the gums. There were no urinary symptoms such as frequency, burning or hematuria. At times there was some diarrhea but no melena.

A diagnosis of hilar tuberculosis, arrested, was made at San Fernando.

The patient lost weight. There was marked atrophy and finally complete loss of sensation below the knees. He was extremely weak. He gave a history of having received some sort of serum injections for asthma in early days. This was probably an autogenous vaccine. He was given three large intramuscular injections. He was admitted to the hospital with many symptomatic diagnoses but no clinical entity. He was sent here for the purpose of a diagnosis.

The physical examination on admission was as follows. Patient was asthenic, markedly undernourished, well oriented and cooperative. Height 66 inches, normal weight 140 pounds, present weight 144 pounds.

Head. Normal conformation. Ears and nose normal. Eyes sclera clear, conjunctiva injected, no ecchymosis noted. Pupils dilated, react normally, rotations normal. Mouth teeth in fair condition, tonsils had been removed, tongue and pharynx normal. No purpuric spots were noted on the mucous membrane.

Neck. No adenopathy. Thyroid not palpable.

Chest. Slender, thin, poorly nourished. Volume and excursion poor. Respirations slightly increased and slightly labored. Resonance impaired over both bases. Tactus increased over right apex. There were many coarse moist bronchial râles throughout the entire chest. There were crepitant râles following expiratory cough in the right apex, a few scattered râles in the left apex.

Cardiovascular. Pulse 88. Blood pressure 100 mm Hg systolic and 60 mm diastolic. Peripheral vessels were soft and compressible. The left border of the heart was 9 cm from the midsternal line in the fifth interspace. The right border was under the sternum. The sounds were of normal rate and rhythm, rather distant, somewhat decreased in intensity. There was slight systolic roughening at the apex, no definite murmurs or thrills.

Abdomen. Soft scaphoid, no masses. The patient complained of more or less general tenderness. Liver and spleen not palpable.

Genitourinary tract. Penis and testes normal. No hernia.

Rectum and Prostate. Normal.

Bones, muscles and joints In general they were markedly asthenic and under-nourished. The legs below the knees showed marked atrophy of the muscles, also the arms revealed more atrophy of the right than of the left. The right wrist and hand were somewhat swollen. There was general muscular and joint tenderness but no apparent limitation of motion. No edema and no cyanosis.

Skin and lymphatics There were purpuric eruptions over the arms, on the body from the nipple line downward, and over both legs. No general adenopathy.

Neurological examination Knee jerks absent, biceps were only slightly present, sensation absent below the knees and apparently reduced in both forearms and hands. Normal response to plantar stimulation.

Roentgenogram of the chest showed nothing remarkable. The urinalysis showed a faint trace of albumin, a few white blood cells, a specific gravity of 1.015. Blood count on August 24, 1934, showed red blood cells 4,53, hemoglobin 80 per cent, white blood cells 24,550, polymorphonuclears 24 per cent, small mononuclears 6 per cent, eosinophiles 70 per cent. Blood Wassermann reaction was negative. Sputum examination showed no tubercle bacilli. Blood chemistry: nonprotein nitrogen 32.4 mg, creatinine 1.2 mg, sugar 66.6 mg. Repeated blood counts during hospitalization showed the red blood cells varying between 3,43 and 4,92, the white blood cells between 33,650 and 16,550, and the eosinophiles between 56 and 71 per cent. On November 22, 1934, fundus examination showed advanced bilateral optic nerve atrophy. Examination by the neurologist on October 31, 1934, resulted in a diagnosis of "peripheral neuritis, etiology unknown."

The patient's course in the hospital was that of progressive failure, with erratic low grade fever. The peripheral neuritis was progressive until the patient was entirely helpless. There was also marked failure in vision. He complained much of joint and muscle pains, and of transitory pains in the precordial region, but there were no typical anginal attacks. There was marked anorexia with considerable digestive disturbance, but no nausea or vomiting. The blood pressure throughout hospitalization ranged within normal limits. On the morning of January 4, 1935, the patient was seen by the Consultant in Medicine (Dr Wm H Leake) who made a tentative diagnosis of periarteritis nodosa, and muscle biopsy was advised. On the evening of January 4, 1935, the patient suddenly became comatose and died a few hours later.

A communication received from the physician who attended the patient for asthmatic symptoms in March of 1933 stated that at that time the eosinophiles varied between 2 and 28 per cent in the differential blood count.

Postmortem record The body was that of a fairly well developed, emaciated white male, properly identified. Body length 160 cm. Body weight about 90 pounds. Hair was brown. Pupils and mouth could not be examined because the body had been embalmed. There was quite marked wasting of the body. There were no external marks or scars of note.

Peritoneal sac There was a very thin pad of subcutaneous fat. Muscles were pale. Peritoneum was smooth. Liver was brown and mottled with grayish plaques, which were evidently fibrotic. The spleen was nodular. The paravertebral and retroperitoneal lymph nodes were all enlarged.

Chest There were no adhesions to the chest plate. Both lungs were comparatively free, with the exception of a few adhesions at the apex, and both were inflated and pink.

Pericardial sac Occupied normal position. Pericardial cavity was obliterated by dense old adhesions of an old healed pericarditis.

Heart Weight 330 gm. On section it was tough, and areas of scar could be palpated in the muscle. Cross section of the heart muscle revealed many scarred areas, more numerous in the left ventricle than in the right, but present throughout the en-

ture heart Scars were perivascularly placed There was no evidence of any valvular lesion There was no endocardial thickening to speak of The coronary vessels were smooth, but the walls were somewhat thickened In some areas there was extensive tissue deposit around the vessels The aorta was smooth throughout Any thickening was around the vessel rather than in the vessel or in the wall

Lungs The combined weight of lungs was about 500 gm They were pale pink There was no emphysema noted There was some fibrosis around the bronchial tree and a chronic bronchitis Mediastinal glands Some were enlarged

Liver Weight about 1300 gm It was brown Capsule was not thickened On section there were small inflammatory scars noted throughout the parenchyma All surrounded the small vessels The larger vessels were also involved Section of the liver showed a thickened scarred periarteritis Gall-bladder was negative

Spleen Weight 140 gm It was nodular, pale, and on section inflammatory scarred nodules were noted throughout

Pancreas Weight 120 gm, there was no gross abnormality

Genitourinary tract Combined weight of kidneys was 400 gm The capsule stripped, leaving a smooth surface Focal scars were noted throughout the parenchyma On section of kidney these were seen to be perivascular in type Adrenals were extremely pale, otherwise negative Bladder, prostate, vesicles and testes revealed no gross pathologic lesion

Gastrointestinal tract No gross pathologic lesion

Brain There were no adhesions between the dura and the calvarium Longitudinal sinus was clear On removal of the dura, the convolutions were flat over the entire brain Brain on section revealed extensive hemorrhage on the left, which had destroyed the greater part of the vital centers at the base The hemorrhage filled the lateral ventricle and had destroyed much of the internal capsular structure It extended beyond the midline into the ventricle on the right The brain weighed about 1600 gm

Vascular system There was an extensive inflammatory reaction involving the vascular tree, more or less confined to the smaller vessels Throughout all the organs and in the peripheral system there was scarring around the vessels, rather than any involvement of the vessel wall or the intima

Anatomical diagnoses (1) Cerebral hemorrhage, left (2) Inflammatory periarteritis, type undetermined (3) Focal scarring, liver, spleen, kidneys, heart (4) Emaciation, severe

Microscopic Examination Stomach, intestine There was quite marked fibrosis in the muscular layers, and there were columns of inflammatory cells breaking the normal muscle coat The cells were mostly eosinophiles, with a few plasma cells and some endothelial cells and young fibroblasts The vessels of the serosa revealed periarterial infiltration of lymphocytes, an occasional eosinophile, many endothelial cells, and many fibroblasts

Lung There was quite marked congestion throughout Collapse in certain area The vascular arterial tree revealed some slight perivascular infiltration and thickening in the adventitial coat Those infiltrating were round cells and an occasional eosinophile, some young fibroblasts and endothelial cells

Second section of lung Revealed peribronchial infiltration of polymorphonuclear and round cells, and patchy infiltration of lung throughout, early bronchopneumonia There was much congestion, and some of the vessels revealed a perivascular infiltration, much less conspicuous, but of the same type as found in the other organs

Brain Section of the cerebral cortex revealed quite marked congestion throughout The vessels of the pia arachnoid showed early perivascular infiltration of round cells and eosinophiles There was marked atrophy of the brain

Second section of brain Revealed a large area of early compression necrosis

Third section of brain There was noted throughout round cell and eosinophile infiltration, in some areas quite diffuse. The vessels of the meninges showed a slight perivascular reaction.

Pancreas The pancreatic parenchyma was fairly well preserved. In the interstitial tissue there was quite marked fibrosis and a perivascular infiltration of eosinophiles, lymphocytes, plasma cells, a few endothelial cells and young fibroblasts, forming large perivascular nodes. In places the wall was encroached upon and the lumen lessened. As a whole, the vascular walls themselves were comparatively free from cellular infiltration. However, some invasion of the same types of cells was noted. Definite nodules were found in places.

Heart Muscle fibers were rather pale. Cross striations were somewhat hazy. The muscle planes in some areas were separated by columns of inflammatory cells made up of round cells, eosinophiles and occasional plasma cells. The vessels showed a perivascular infiltration of inflammatory cells, the greater number of which were eosinophiles. There were a few plasma cells and a number of round mononuclear cells and young fibroblasts. One vessel revealed partial destruction of the wall and a clump of the same type cells in the lumen. There were some cells in the muscular coats in certain regions. All surrounding fat was infiltrated, and there was definite organization in places, forming early scars. The vascular walls in places were infiltrated, but for the most part the muscular layers were clear and the greater part of the infiltration was perivascular, rather than involving the wall. There was practically no evidence of arteriosclerosis.

Second section of heart muscle Revealed very extensive perivascular infiltration of inflammatory cells and fibrosis. The cells in the other sections were made up mainly of eosinophiles, a few lymphocytes, plasma cells, endothelial cells and young fibroblasts. There was definite nodule formation around the vessels. Muscle fibers were rather pale. Striations were hazy.

Spleen There was diffuse fibrosis throughout. Lymphoid areas were extremely small. The splenic sinuses were practically obliterated. Some areas were noted in which eosinophiles and plasma cells predominated.

Kidney Tubular epithelium was quite markedly swollen and cloudy. Some scarring in the cortical region was noted, probably vascular in origin. There was a perivascular infiltration, with early fibrosis, involving nearly all of the vessels. The infiltration was made up mostly of eosinophiles, some lymphocytes, a few plasma cells, endothelial leukocytes and young fibroblasts. The infiltration was nearly all perivascular in type, although certain areas were noted in which the wall was invaded. The infiltration formed a definite nodule surrounding the vessels.

Liver Liver cord cells were rather pale. Some contained pigment. The sinuses were rather wide, especially around the central veins. The portal areas showed some proliferative changes in the biliary capillaries. The arteries in the portal areas revealed some perivascular infiltration of round cells and an occasional eosinophile. Reaction in the liver was not as marked as in most other sections studied.

Aorta Revealed the wall to be well preserved. The markings were essentially normal. No perivascular infiltration was noted.

Section of femoral vessels The large artery revealed practically no thickening of the wall, and normal relationship was practically preserved. The smaller vessels, however, showed an infiltration, mild in character, made up of a few eosinophiles, lymphocytes and plasma cells. The reaction was not nearly so marked nor so conspicuous as in most of the other sections studied.

Microscopic diagnoses (1) Periarteritis nodosa (2) Compression necrosis, cerebral, following hemorrhage (3) Cloudy degeneration, liver, kidney (4) Fibrosis, heart (5) Myocardial degeneration.

Case 2 G. P., a 47-year-old cook, was first admitted to the hospital on December 17, 1937. At that time he was complaining of weakness, general aches, pain and

weakness of all extremities, and fever. About a week prior to admission he had apparently caught cold, with general malaise, general muscular and joint aching, and slight gastrointestinal distress. The latter cleared up but the weakness and general body aches continued. During hospitalization he ran a temperature which varied from 99° F to 101.5° F. The general physical examination showed nothing remarkable. Heart rate was 110, regular, sounds were of good quality, no murmurs. The blood pressure varied from 132 mm Hg systolic and 86 mm diastolic to 180 mm systolic and 100 diastolic at time of discharge. There was slight tenderness in the epigastrium, but no abnormalities were found. There was tenderness over the muscles of the calves along the course of the nerves. The deep reflexes of the legs tended to be reduced. There was a mild pharyngitis present. Flat plate of the abdomen, gall-bladder visualization and roentgenogram of the chest showed nothing remarkable. The urea nitrogen was 11.2 mg per 100 cc. Three blood cultures were negative. Blood Wassermann and Kahn reactions were negative. Urine examination was not remarkable. White blood count varied from 13,200 to 15,200, polymorphonuclear leukocytes 80 to 90 per cent. On one count two eosinophiles were noted. Stool examinations and cultures disclosed nothing abnormal. Two agglutination tests were as follows: Typhoid, positive 1/480 and 1/240, paratyphoid A, positive 1/240 and 1/120, paratyphoid B, positive 1/60 and 1/60. Agglutination tests with *B abortus*, *B melitensis* and *P tularensis* were negative. The patient left the hospital against advice on January 28, 1938. Up to that time a definite diagnosis had not been made. In spite of the positive typhoid agglutination tests, it was not thought that he had this disease. A diagnosis of periarteritis nodosa was considered and a biopsy contemplated, but owing to the patient's sudden departure it was not completed.

The patient was re-admitted to the hospital on February 8, 1938. At that time he showed a beginning bilateral wrist and ankle drop with marked weakness of the legs and hands. Blood pressure was 180 mm Hg systolic and 120 mm diastolic. Heart rate was 110. He complained of extreme weakness, and shortness of breath. There was a mild ankle edema. He also complained of some vague precordial pain at times. His course in the hospital from this date on was gradually downward. He had a fever of from 99.5° F to 101° F with occasional short periods during which he was afebrile. The peripheral neuritis was rapidly progressive, and the patient was helpless during most of his hospitalization. The terminal blood pressure was 190 mm Hg systolic and 130 mm diastolic.

Examination showed a progressive hypertensive retinitis, which toward the end greatly impaired the vision. No specific arterial lesions were seen in the retina. On the second admission the agglutinations for typhoid were negative. Blood urea on admission was 12.9 mg per 100 cc but rose gradually, and on April 15, 1938, blood urea was 31.2 mg and creatinine 3.2 mg. On May 10, 1938, nonprotein nitrogen was 53.5 mg. The red blood cell count varied between four and five million, and the white count between 14,000 and 15,000 with approximately 80 per cent polymorphonuclears. Lymphocytes were not above 2 per cent. A biopsy of the gastrocnemius on February 27, 1938, showed the typical picture of periarteritis nodosa. The edema present on admission rapidly cleared, but on March 20, 1938, the patient began to develop nocturnal dyspnea, which was followed by a recurrence of edema, and from this time on the course was that of progressive heart failure. A few days before death the patient showed some petechial hemorrhages over the extremities. He died on May 21, 1938. Autopsy was refused.

Pathological Report on Muscle Biopsy. Gross specimen consists of two small pieces of gastrocnemius muscle, the largest measuring 1.5 by 1.0 by 0.6 cm.

Section shows rather extensive perivascular changes. A moderate to marked perivascular fibrous proliferation is present. Fibrin laid in the lumen are varying numbers of leukocytes and numerous phagocytes. Scattered eosinophiles are also present. Occasional granules of brown perivascular pigment in perivascular tissue.

PERIARTERITIS NODOSA

Contained in the media of the larger arterioles are collections of pale histiocytes forming pseudo tubercles. In these vessels the endothelium is swollen and subintimal tissue is thickened and homogeneous.

In other vessels a marked fibroblastic intimal thickening is present, resulting in obliteration of the lumen. Such lesions show varying degrees of hyalinization. Histologically the lesions are typical of periarteritis nodosa (gastrocnemius muscle).

As previously emphasized the disease is comparatively rare. Still in 1928 found 142 cases reported, of which only 21 were in the English language. Powell and Pritchard² in 1932 gathered 150 cases from the literature. Up to the present time approximately 200 cases have been published. The diagnosis was established before death in a comparatively small number of these cases. Middleton³ in 1934 reported only 34 cases in which the diagnosis was made before death. Spiegel⁴ states that approximately 12 per cent of the cases have been diagnosed by clinical study during life. Furthermore, in this small percentage of cases the diagnosis was uncommonly established by the routine pathological examination of surgical specimens to the surprise of the clinicians. It is apparent from a review of the literature that accurate diagnosis on the basis of clinical study alone is unusual.

The pathology of this condition has been discussed fully by several authors^{3,5,6}. Briefly it may be stated that the fundamental pathological change is an inflammatory lesion predominantly involving the medium-sized arteries and usually focal in character. There has been discussion as to the manner of involvement of the vessel wall. Ophuls⁶ believed that the vessel was invaded through the lymphatics of the adventitia and that the media was first to be destroyed. The elastic intima is soon involved in the process. Inflammatory cells which invade the involved area are principally polymorphonuclear cells, though eosinophiles and some lymphocytes are also present in most cases. The remaining arterial wall may become involved in varying degrees with spread to the perivascular tissue. Periarterial nodules, which the disease assumes its name, may be formed. When these are present in the subcutaneous arteries they may serve as an important diagnostic factor. The pathologic process may spread to the larger arteries, the arterioles and capillaries, and very rarely to the veins.

Following the vessel injury several events may occur, e.g., aneurysm formation, rupture and hemorrhage, thrombosis and perivascular inflammation. The distribution is generalized, though in some cases the process has been quite localized. Kernohan and Woltman,⁷ who have described the involvement of the nervous system very completely, reported a case limited to nerves of the extremities. Arkin who has discussed the pathology of periarteritis nodosa very completely divides the process into four stages: the alterative degenerative stage, the acute inflammatory stage, the granulation stage, and the healed stage. Lesions in all stages may be found in generalized involvement. Harris and Freidricks⁸ have divided the pathological process into three stages from the point of view of the clinical picture.

festations first stage, injury to vessel wall, second stage, result of vessel wall injury—aneurysm, hemorrhage and thrombosis, and the third stage, infarction of the tissues supplied by the involved vessels. There is apparently no tissue which can be considered immune to involvement, and it is this fact which is responsible for the protean clinical manifestations.

The problem of etiology is considered of paramount importance in any disease and in this particular disease it has received a great deal of attention. However, so far as I have been able to ascertain, no definite facts have been obtained.

As is usual with diseases of inflammatory nature, syphilis was early considered a factor.⁵ There is apparently no reliable basis for this, as associated syphilis has been found in only a small percentage of cases and no definite evidence of infection has been demonstrated in the lesions.

Inherent vascular weakness, as well as reflex vascular mechanisms, has received theoretical consideration.

Allergy has also been given serious consideration as a possible factor. This is not unreasonable when one considers some of the cases reported which, like my first case, have outstanding clinical characteristics which are generally conceded to fall into the group of allergic manifestations. However, there are many cases which do not present either objective or subjective characteristics which may be considered to be of this nature. Generalized vascular lesions are well recognized as being associated with or being the result of the allergic state. A recent paper by Clark and Kaplan⁶ is of interest in this respect. Two patients died following severe manifestations of serum sickness due to antipneumococcus serum. Widespread vascular lesions were found. These were very suggestive of periarteritis nodosa. On reviewing the literature on this subject one is impressed with the frequency of allusions to allergy.

The possible relationship to rheumatic fever has received considerable attention in the literature by some authors. Ophuls⁷ suggested that it might be a subacute rheumatic manifestation. Friedburg and Gross¹⁰ reported finding Aschoff's bodies in the myocardium of two out of five cases examined post mortem and emphasized the importance of a rheumatic history. Spiegel⁸ reports that evidence of rheumatic endocarditis was found in four of 17 cases. Neale and Whitfield,¹¹ and also Rothstein and Welt,¹² discuss this relationship. Von Glahn and Pappenheimer,¹³ however, in their studies on rheumatic arteritis found that it has characteristics distinctly different from the lesions of periarteritis nodosa. It has not been my impression that a rheumatic history or definite co-existing pathologic lesion of rheumatic type has been generally present in the cases reported in the literature. One can certainly not be dogmatic as to the etiological significance of rheumatic fever at the present time.

A point of primary importance at the present time is to determine whether this disease is specific from an etiological standpoint or possibly a post-infectious allergic reaction on the part of the individual to any one of, or a

combination of, various etiological factors. In this connection the paper of Harbitz¹⁴ is of interest. He discusses the fact that the generalized inflammation and necrosis of focal type have been described in the small arteries in many conditions, such as scarlet fever, diphtheria, carbon monoxide poisoning, typhus, influenza and suppurative processes. Though these findings are similar to periarteritis nodosa he believes that periarteritis is a clinical entity with a specific etiology, probably a virus. Sigmund¹⁵ reports that 20 per cent of 165 cases of streptococci sepsis showed mycotic aneurysms. Hall¹⁶ in discussing the vascular lesions produced by acetylcholine injection in animals has noted a pathological condition in the mesenteric vessels quite typical of periarteritis nodosa. Lesions typical of periarteritis nodosa have been described in a case of disseminated lupus erythematosus¹⁷.

Investigation of bacteriological nature with reference to etiology has been carried out by several workers, Klotz,¹⁸ Lamb,¹⁹ and Harris and Freidricks,⁸ but nothing was established in this respect. Harris and Freidricks concluded it was of virus etiology based upon the inference of the negative bacteriological findings. Arkin⁵ believes that the disease is a definite clinical entity, however, and that the etiology is probably a virus. This seems to be the generally approved opinion at this time. It seems that periarteritis nodosa is an important factor in the confusion which exists in the broader subject of arteritis in general.

As to the clinical manifestations, the most striking fact is the wide variability of the symptoms and clinical findings. Harbitz²⁰ has divided the cases into groups, depending upon the nature of the clinical findings, i.e., cerebral, neuromuscular, gastrointestinal, cardiac, and cutaneous. To this classification should be added the pulmonary group.

The age of the patient may vary between a few months and 80 years. The disease most commonly occurs between 20 and 40, and is usually found in a male.

The patient usually presents the picture of subacute sepsis, fever of from 99 to 102° F. being most common. There may be remissions of the fever, and afebrile cases are reported in the literature.

The blood shows abnormalities in all cases. Leukocytosis is usually present. This averages from 10,000 to 60,000 cells. Eosinophilia is a prominent characteristic of the blood picture in a portion of the cases, as illustrated in Case 1. Anemia of a moderate degree may be present. Nothing significant has been disclosed by blood cultures.

The general symptoms common to sepsis are present, i.e., anorexia and loss of weight and energy. Tachycardia is commonly marked. An occasional case departs from the general description by running a rapid fulminating course. Further than this the individual characteristics of any case will depend upon what system and organs are predominantly involved in the pathologic process.

Involvement of the nervous system is evident in a considerable number of cases. Peripheral neuritis is frequently noted and is rapidly progressive.

Many symptoms described as myositic or rheumatic are also probably due to milder degrees of neuritis. Neuritis has been considered a toxic manifestation by some but Kernohan and Woltman⁷ have recently described true infarcts in the peripheral nerves. This syndrome has been described by several writers. In Haining and Kimball's case²¹ it was due to an associated pneumococcic infection. In Bennett and Levine's case²² no meningitis was found post mortem, whereas a true leptomeningitis was found by Krohulik et al.²³ Cerebral hemorrhage may occur as in Case 1, but this is uncommon.

Cardiac manifestations are very common owing to coronary artery involvement. Both acute infarction and hemorrhage may occur, or there may be progressive congestive failure. Anginal attacks are not infrequent. Arrhythmias may occur, and electrocardiographic findings have been described by Master and Jaffe.²⁴

Pulmonary symptoms are more rarely noted. Occasionally these may be very marked, as illustrated in Case 1. Bronchitis with asthmatic attacks is the most common pulmonary manifestation. Herrman²⁵ has described the roentgenological findings of pulmonary periarteritis nodosa.

That gastrointestinal symptoms and findings of some nature are usually present is evident from reading case reports. Meyer first described this condition as chlorotic marasmus because such symptoms were so consistently present. Ulceration of the stomach, hemorrhage, or perforation may occur. Symptoms may resemble those of peptic ulcer, gall-bladder dyspepsia, or ulcerative colitis. Felsen²⁶ has discussed findings by sigmoidoscopic examination in this condition. He states that the small arteries of the bowel wall may show hemorrhage, thrombosis or aneurysmal dilatation. He believes that the diagnosis might be made from such findings but as far as I know this has not been done. Attacks typical of appendicitis may occur and operation has been performed with this pre-operative diagnosis.

Liver involvement may lead to infarction, intra- or extrahepatic hemorrhage, or may simulate cirrhosis or common duct stone.

Renal involvement is most consistently found, occurring in approximately 80 per cent of the cases. There may be acute hematuria resembling that in the case of stone, tumor or essential hematuria. Acute hemorrhage into the perirenal tissue may occur.²⁷ More commonly there is the picture of progressive renal failure with rise in blood pressure and terminal uremia. This may progress quite rapidly and clinically present a picture compatible with malignant hypertension. Cases of this type have been described by Friedburg and Gross,² Wordley,²⁸ and Keegan.²⁹ It is possible that in the past some cases considered to be malignant hypertension may have been of this type. The possibility of periarteritis nodosa should be thought of in such a case.

far as I know the diagnosis has not been made by this means. Rarer ocular manifestations are iridocyclitis and episcleritis. Optic atrophy as it occurred in one of these cases is apparently quite rare. King³² reported optic atrophy in one eye in a case of periarteritis nodosa.

Skin manifestations are not usual in cases so far reported, but occasionally they are very impressive. Schottstaedt³³ states that involvement of the skin is present in 20 per cent of the cases. The findings include urticaria, ecchymoses, nodules, ulcerations and gangrene of the skin. While considering skin lesions it is of interest to note that the combined descriptions of Schoenlein's and Henoch's purpura conform very well with the characteristics of periarteritis nodosa. In Singer's case³⁴ a pre-operative diagnosis of Henoch's purpura was made, and my first case was considered one of Schoenlein's purpura for some time.

As has been previously noted⁴ there is great similarity in the case reports of the so-called "erythema group of diseases" and periarteritis nodosa. The outstanding clinical features of this group were purpura, gastrointestinal symptoms and nephritis^{35, 36, 37}.

It is apparent that clinical diagnosis depends upon keeping this condition in mind when considering cases of bizarre and apparently unrelated clinical manifestations, particularly cases of subacute sepsis. Diagnosis may be definitely established clinically by muscle biopsy which was first used by Kussmaul. It is obvious that in some cases, particularly in the more localized types, this will not be of assistance. Eosinophilia should also direct attention to this disease.

The prognosis seems to be fatal in the majority of cases. Carr³⁸ and Arkin⁵ have discussed the possibilities of recovery. It has been estimated that 10 per cent of the cases may heal. In those cases reported which have been diagnosed ante mortem one is impressed with the consistency of fatal termination, even though the clinical course may be of several years' duration³⁹. Schottstaedt³³ has reported a case which was arrested while under observation. In general the outlook is extremely grave when this diagnosis has been established.

Therapy has been of no specific value. In Case 2 sulfanilamide was given over a considerable period of time. Also, upon the suggestion of Kerr,⁴⁰ vitamin C was given in large doses for several weeks. Needless to say no clinical results were evident.

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ELECTROCARDIOGRAPHIC CHANGES IN OLD AGE*

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CONSIDERABLE information has recently been published on the various problems of old age. Particular attention has been focused on the cardiovascular system, since its life cycle, important in itself, is frequently the determining factor of the functional age of all the vital organs.

Attempts have been made to define the "normal" and the "abnormal" in the aging process of the cardiovascular system but as yet there is no agreement as to "where to draw the line between phenomena of pure senescence and those of superimposed disease."¹ The reasons for this difficulty are various. One obvious factor, at least as far as the electrocardiogram in old age is concerned, is the rather scanty amount of carefully analyzed statistical information. Another reason is the lack of uniformity in the criteria employed. It is because of certain individually preconceived criteria that one report² gives the incidence of abnormal electrocardiograms in the aged as 55 per cent, whereas another study³ concedes only 26 per cent. Two distinct points of view oppose each other: (1) the electrocardiogram in the aged has more or less special features of its own,⁴ and (2), it has no characteristics that distinguish it from that of younger persons.^{1,5} It appears that the latter view has received increasing support in the recent literature and was, therefore, adopted in the evaluation of the electrocardiographic findings in our present report. This study, in addition to furnishing statistical data on the subject, has also the following advantages: (a) it does not deal with hospital material, and, therefore, possibly approaches more or less the "door to door census type" of investigation, (b) it deals with a single racial group and may thus serve the purpose of comparative studies.

Material. The material consists of 300 ambulatory men and women of the Hebrew race, between the ages of 60 and 100 years, admitted to the Home of the Daughters of Israel for social and economic reasons. The Institution as a rule admits "aged persons, able-bodied and ambulatory, with no infirmities, and requiring only general medical, periodic supervision and occasional attendant care." Many of the inmates are engaged in some light occupation on the premises; a number of them do heavier work, such as laundry; a few of the inmates go about their business in town, returning to the Institution at the end of the day. No one performs very hard work and no one is required to climb stairs. Although none is admitted with evidences of congestive failure, some inmates eventually become bedridden because of advanced failure. Such cases, however, were not included in our study. Nor were bedridden cases suffering from any illness other than

heart disease included. The vast majority presented thickening of the radial, temporal or dorsalis pedis arteries. None of the inmates had a history of rheumatic heart disease or syphilis. Only one had a positive blood Wassermann reaction.

Clinical observations over a period of several months were made on all cases included in the study. Thirty-three of the 300 cases presented, on occasions, evidences of mild failure easily controlled by a short period of bed rest. Several blood pressure readings were recorded for each inmate and the average was used in this study. Fluoroscopic studies were made in accordance with the criteria of the New York Heart Association.⁶ Esophagograms were done in a large number of cases. Electrocardiograms were taken in the recumbent position. The fourth lead used was IV F.

RESULTS

Age and Sex. There were 140 males and 160 females. There was a slight preponderance of females in every decade. The tenth decade consisted of males only. About 15 per cent were in the youngest age group (60-69). There were only two inmates below the age of 65 and they were the only ones with a history of coronary thrombosis prior to admission.

Blood Pressure. In considering the question of hypertension, it was thought advisable to divide the hypertensives into two groups: those with a systolic tension exceeding 140 mm Hg, the diastolic remaining below 90 mm — *systolic group*, and those with a diastolic tension exceeding 90 mm — *diastolic group*. In the diastolic group the systolic pressure was always above 140, the average systolic tension being 191.2. In the systolic group the average systolic tension was 169.1. Nine cases had a diastolic tension of 120 plus, 34 had a systolic tension of 200 plus.

Of the inmates 23.3 per cent had a normal tension, 32.3 per cent belonged to the systolic hypertensive group, and 44.4 per cent belonged to the diastolic group. The incidence of hypertension was approximately the same in all age groups.

TABLE I
Distribution of Tension and Heart Enlargement in Relation to Age

Age	Non-Hypertensives		Systolic Hypertensives		Diastolic Hypertensives		Total	Total Hypertensive		Total Enlarged Heart	
	E H	No E H	E H	No E H	E H	No E H					
60-69	3	8	9	5	10	9	44	33	75%	22	50%
70-79	14	22	34	18	58	21	167	131	78%	106	63.5%
80-89	11	10	19	11	24	8	83	62	77%	54	65%
90 plus	—	2	1	—	2	1	6	4	66%	3	50%
Total	28	42	63	34	94	39	300	230	(76.7%)	185	(61.6%)
	70 (23.3%)		97 (32.3%)		133 (44.4%)						

Fluoroscopy. One hundred eighty-five cases or 61.6 per cent had fluoroscopic evidence of enlargement of the heart. The incidence of enlargement seemed to increase with age. This was particularly true for the nonhypertensive group in which 40 per cent of the cases presented enlargement. In the systolic hypertensive group 65 per cent, and in the diastolic group 70.6 per cent had enlarged hearts (table 1).



All but three cases presented evidence of sclerosis of the aorta. There was a definite relationship observed between the degree of elongation, dilation, tortuosity or density of the aortic shadow and the age of the inmate (figure 1)

Stethacoustics Forty-one cases had systolic murmurs at the apex and base. Thirty had a systolic murmur at the base only, 19 at the apex only. Sixty-four out of a total of 71 with systolic murmurs at the base presented marked sclerosis of the aorta. Forty-two out of 60 with a systolic murmur at the apex had heart enlargement.

Out of the entire series of 300 cases, only 96 presented murmurs over the precordium. Three subjects had a diastolic murmur at the base, they were 80, 81 and 83 years old. Their blood pressure readings were 140 mm Hg systolic and 60 mm diastolic, 130 systolic/80 diastolic and 150 systolic/80 diastolic respectively. One had no enlarged heart, one had two plus enlargement and one three plus enlargement. One inmate, 80 years of age, presented a double murmur at the apex with no heart enlargement and a blood pressure of 180 mm Hg systolic and 80 mm diastolic. The second sound at the aortic area was accentuated in 20 cases, of which all but one had hypertension.

The Electrocardiogram There were 200 abnormal tracings and 100 normal ones. The types of electrocardiographic abnormalities are listed in table 2. Premature contractions are included as an abnormality. Although

TABLE II
Type of Electrocardiographic Abnormalities

	No. of Cases	Percentage
Sinus arrhythmia	5	
Auricular fibrillation	12	4%
Auricular flutter	2	
Premature auricular contractions	17	
Premature ventricular contractions	15	
Premature auricular contractions and premature ventricular contractions	4	
Premature auricular contractions and premature nodal contractions	1	
Premature nodal contractions	1	
Premature contractions	38	12.7%
Paroxysmal nodal tachycardia	1	
Paroxysmal ventricular tachycardia	1	
Complete A-V block	1	
Prolonged PR interval	40	13.3%
Prolonged I-V conduction	39	13%
T ₁ changes	44	
T ₂ changes	10	
T ₁ and T ₂ changes	34	
T ₁ changes alone	13	
T changes	101	33.6%
RST segment depression	63	
Notching in Lead I or Lead II	17	
Notching or slurring in more than one lead	26	
Notching and slurring	43	14.3%
High voltage	3	
Low voltage	11	
Short or absent initial upward deflection in Lead IV	9	
Q ₂ deep	5	
Q ₃ deep	9	
Q ₂ and Q ₃ deep	4	

in the young subject they are frequently considered functional, in the old they may be indicative of a degenerative process

Rate The results in our study are contrary to the belief that heart rate decreases with age.⁷ Nineteen cases had a rate of 60 and below. Two hundred thirty-two had a rate between 60 and 100. Forty-nine, or 16 per cent, had a tachycardia. A higher ventricular rate was noted in the female population. The rates stated are those recorded in the electrocardiograms and not the average rate obtained on clinical examinations.

Rhythm Fifty-nine cases, or 20 per cent of the group presented an arrhythmia. There were five cases of sinus arrhythmia. Twelve cases, or 4 per cent, showed auricular fibrillation. There were 38 cases, 12.7 per cent, with premature contractions about equally divided between premature auricular and premature ventricular contractions. The incidence of premature contractions seemed to be definitely greater in the hypertensive group. There were 30 such cases in this group and only eight in the nonhypertensive group. In 26 cases premature contractions were associated with other electrocardiographic abnormalities. To consider them as functional changes under the circumstances would hardly be proper. In only 12 cases premature contractions were the sole abnormality in the tracing, the majority of them being of auricular origin.

QRS Complex Left axis deviation was seen in 213 cases (71 per cent). Two cases (0.7 per cent) showed right axis deviation. Eighty-five cases presented no axis deviation. Seventy per cent of this group had hypertension about equally distributed between the systolic and diastolic groups.

In the left axis deviation group, two out of every three inmates had heart enlargement. The group with no axis deviation was equally distributed between those presenting heart enlargement and those not showing enlargement. The two cases with right axis deviation had normal sized hearts. Right axis deviation was, therefore, not considered an abnormality.⁸ High voltage electrocardiograms were seen in only three cases (1 per cent) in spite of the predominance of hypertension in our series. Low voltage was noted in 11 cases (3.6 per cent).

Notching in I_1 or I_2 occurred in 17 cases. Notching or slurring in more than one lead occurred in 26 cases. Deep Q_2 was observed in five cases, deep Q in nine cases, deep Q_2 and Q_3 in four cases. There was no history of acute coronary insult in any of these cases. Short or absent initial upward deflection in I_1 occurred in nine cases. Only two of them did not have hypertension.

TABLE III
Incidence of Conduction Difficulties

Age	Total Number	A-V	Percentage	I-V	Percentage
60-69	44	3	6.8%	2	4.5%
70-79	167	20	12%	22	13.2%
80-89	83	14	16.9%	14	16.9%
90 plus	6	3	50%	1	16.7%
Total	300	40	13.3%	39	13%

RST Segment Downward displacement of the RST segment occurred in 63 cases, the great majority of which belonged to the hypertensive group equally distributed between the systolic and diastolic subdivisions

T-Wave Changes One hundred and one cases (33.6 per cent) presented isoelectricity or inversion of the T-wave. T-wave changes in Lead I only occurred in 44 cases. Thirty-four cases had T₁ and T₂ changes simultaneously. T₂ changes alone occurred in 10 cases. T₄ changes occurred in 13 cases. There is an appreciable rise in the incidence of T changes with age (table 4)

TABLE IV
T Changes in Relation to Age

Age	Total Number of Cases	T Changes	Percentage
60-69	44	13	29.6%
70-79	167	55	32.9%
80-89	83	30	36.2%
90 plus	6	3	50%

The distribution of abnormal electrocardiograms in various age groups is shown in table 5. The incidence of electrocardiographic abnormalities decidedly increased with age.

TABLE V
Electrocardiogram in Relation to Age

Age	Normal	Electrocardiogram	Abnormal	Electrocardiogram	Total
60-69	21	47.7%	23	52.3%	44
70-79	56	33.4%	111	66.6%	167
80-89	21	25.3%	62	74.7%	83
90 plus	2	33%	4	67%	6
Total	100	33.3%	200	66.7%	300

Table 6 presents the relationship between heart enlargement and type of tracing. One hundred eighty-five cases presented enlargement. Seventy-four per cent of this group had abnormal tracings. Of the 115 cases with no enlargement, 62 cases or 53.9 per cent had abnormal tracings. In the

group with abnormal electrocardiographic findings 69 per cent showed enlargement of the heart, whereas in the normal group 47 per cent showed enlargement

TABLE VI
The Relationship of Heart Size to Type of Electrocardiogram

Age	Heart Enlargement		No Heart Enlargement		Total
	Norm E C G	Abnorm E C G	Norm E C G	Abnorm E C G	
60-69	5	17	16	6	44
70-79	30	76	28	35	167
80-89	11	43	10	19	83
90 plus	1	2	1	2	6
Total	47 (26%)	138 (74%)	53 (46 1%)	62 (53 9%)	300

The relation of the type of electrocardiogram to tension is seen in table 7 In the normal group 68 per cent had an elevated blood pressure In the abnormal group 78 per cent showed hypertension

TABLE VII
Type of Electrocardiogram and Tension

Normal Electrocardiogram			Abnormal Electrocardiogram		
Hypertension		Normal Tension 			

There were 42 inmates with no hypertension and no enlargement of the heart Fifty-five per cent of this group showed abnormal electrocardiograms

Mortality Rate in Relation to the Abnormal Electrocardiogram. Of the 300 cases studied, 30 or 10 per cent died within six months from the time that the electrocardiograms were recorded This is the average death rate for the Institution, based on statistics for the past several years Twenty-seven of the 30, or 90 per cent of the mortality group, had abnormal electrocardiograms Twenty-one or 70 per cent had abnormal T changes The immediate cause of death was pneumonia in 13 cases, cerebral thrombosis in four, secondary chorea in one and acute pulmonary edema in six The causes of death in the remaining six were head injury, uremia, ileus, carcinoma of peritoneum (two cases)

DISCUSSION

Blumgart and his co-workers⁹ in a series of 355 cases examined pathologically observed many normal hearts with little or no coronary arteriosclerosis or other abnormalities in patients over 70 years of age. However, the generally accepted view is that some degree of circulatory disturbance exists in all hearts of senescence. Bosk¹⁰ emphasized the existence of a parallelism between sclerosis of the aorta and coronaries. Postmortem records of 381 cases of 70 years and older reported by Willius¹¹ revealed some degree of coronary sclerosis in all cases, although only 12.6 per cent of the group reported died of heart disease. It is, therefore, not surprising to find a predominance of abnormal electrocardiograms in old age. The age at which abnormalities appear in apparently healthy persons is rather early. In a recent study Johnson¹² reviewing 2400 electrocardiograms of apparently healthy males of an average age of 47.8 years, found 10.4 per cent of the tracings to be definitely abnormal. The percentage would be higher if some of his "borderline tracings," those with depressed RT segments and isoelectric T_{1,2} were included. It is apparent from this report, as well as from our study, that clinical evidences of heart disease are not essential for electrocardiographic abnormalities to be present.

The rôle of hypertension as a causative factor of abnormal changes in the electrocardiogram is well known. In the younger group, reported by Johnson,¹² the systolic and diastolic hypertensives were found six and seven times, respectively, as frequently in the abnormal group as in the normal. Our series is predominantly hypertensive. However, 78 per cent of the abnormal electrocardiographic group had hypertension as against 68 per cent in the normal group—a difference not wide enough to account for the incidence of abnormal electrocardiograms. Heart enlargement seems to be more definitely correlated. In the abnormal group there was a predominance of enlarged hearts. However, hypertension and heart size are not the only factors. Forty inmates presented normal sized hearts and normal tension, and yet more than one half of them had abnormal tracings. The distribution of the abnormal tracings in relation to age follows more definitely an ascending line. This fact is particularly conspicuous in the analysis of some of the individual abnormalities encountered in our study, i.e., the conduction difficulties and T-wave changes.

The significance of the individual abnormalities in the electrocardiogram is a matter of controversy. Sinus arrhythmia is said to be common in the young age groups as well as in the old. This phenomenon is supposed to be due to vagus activity. There were only five cases of this arrhythmia in our study and in three cases this manifestation was associated with other electrocardiographic abnormalities. In the remaining two cases the sinus arrhythmia was not dependent on the respiratory phase and was gross. "In sinus arrhythmias which are not induced by respiration, the suspicion is justified that an organic disease of the sinus node exists."¹³ We believe that this

rather uncommon finding in old age electrocardiography is an expression of circulatory disturbance

Of the same order is the prolongation of the PR interval. Six cases of first stage A-V block were given atropine sulphate, grains $\frac{1}{30}$ intravenously. In only one case was the PR interval of 0.24 second reduced to 0.20 second. A PR interval of 0.40 second was reduced to 0.28 second, 0.24 to 0.22 second, etc. Thus, the prolongation of A-V conduction was not altogether due to increased vagus tone.

The significance of premature contractions in old age has not been definitely ascertained. In our study the majority occurred in conjunction with other abnormal electrocardiographic changes, and one is inclined, therefore, to attach to this arrhythmia the significance of a pathological finding. It has been stated that premature auricular contractions occur more often in the aged and are, therefore, organic, whereas premature ventricular contractions are more frequently encountered in youth and are, therefore, functional.¹⁴ However, opinions to the contrary have also been expressed. "The ventricles (in old age), it appears, give rise more frequently to premature contractions than the auricles" (see also Duthoit et al.¹⁵). The possibility that this arrhythmia, as well as other cardiac arrhythmias, develops because of a disparity between the mass of the heart and the coronary blood supply has been expressed by Wagenfeld.¹⁶

The only change in the electrocardiogram of senescence which cannot be explained by disease of the myocardium is the tendency to left axis deviation. This change has an anatomical basis in the elevation of the diaphragm in the aged, causing the heart to assume a horizontal position. There is no reason to believe, as some authors do,³ that auricular fibrillation and the prolongation of the PR interval are functional in nature. Auricular fibrillation in the old is usually of the slow type, the slow rate being due to A-V block. No matter what the pathogenesis of the fibrillation is, the A-V block implies associated myocardial involvement. The exclusion of auricular fibrillation and A-V block from the list of important abnormalities naturally reduces the incidence of abnormal electrocardiograms considerably. We cannot agree with Levitt,³ who concludes from his study of 100 cases of 71 years and over that only about "25 per cent of apparently healthy men and women over the age of 70 probably have considerable myocardial damage."

A recent paper by Eliaser and Kondo¹⁷ gives a very high incidence (85 per cent) of abnormal electrocardiograms in the aged. The authors admit that it may, if not all, of the electrocardiographic changes are probably the result of minor silent coronary occlusions, but certain of these changes, namely left

sidering abnormalities by the normal standards as normal for senescence lies in the possible avoidance of error in the diagnosis of acute coronary insults, but their significance as evidences of sometimes extensive, slowly progressing myocardial damage should be more emphasized

The existing confusion on this subject might possibly be obviated if one would consider an abnormal electrocardiogram abnormal for both young and old. In the old, the abnormal electrocardiogram may be compatible with "healthy" clinical behavior, as physical activities are limited in that group. Abnormal clinical behavior in association with abnormal electrocardiograms in the young is an expression of the amount of activity in that age period.

The observation that 90 per cent of our mortality group had abnormal electrocardiograms is probably of significance. It is a relationship of 9 to 1 as against 2 to 1 in the entire series. We consider this point to be supporting evidence of the assumption that abnormal electrocardiograms in the aged are indicative of myocardial damage, in spite of the fact that a small number of those who died can be said to have had cardiac failure as the primary cause of death.

Whether the racial factor present in our group has any bearing on our results cannot be stated at this time. More comparative studies are necessary to establish the possibility that this factor may influence vascular changes and consequently changes in the electrocardiogram.

SUMMARY

A group of 300 ambulatory cases of Hebrew extraction were studied to determine the incidence of abnormal electrocardiograms in old age. Clinical, as well as fluoroscopic, examinations were performed and an attempt was made to correlate the incidence of the electrocardiographic abnormalities with the anatomical and functional status.

Of a total of 300 inmates, 44 belonged to the seventh decade, 167 to the eighth, 83 to the ninth and six to the tenth. All had evidences of peripheral arteriosclerosis, and all but three had fluoroscopic evidence of sclerosis of the aorta. Enlargement of the heart was noted in 62 per cent of the cases. Twenty-three per cent had a normal blood pressure reading, 32 per cent showed an elevation of the systolic tension only, and 45 per cent showed both systolic and diastolic elevation.

There were 100 normal tracings and 200 abnormal ones. The normal tracings were about equally distributed between those showing enlargement of the heart and those presenting a normal sized heart. In the group with abnormal electrocardiograms the relation between the number of inmates having enlargement and the number with normal sized hearts was 2-1. Sixty-eight per cent of those with normal electrocardiograms showed hypertension. In the group with abnormal electrocardiograms, 78 per cent presented hypertension. There were 40 inmates with no hypertension and no cardiac enlargement. Fifty-five per cent of this group showed abnormal

electrocardiograms The incidence of abnormal electrocardiograms increases with age as does the occurrence of heart enlargement Hypertension does not follow the same line The incidence of T changes shows a definite rise with age

The coexistence of an abnormal electrocardiogram with an apparently normal clinical behavior in the old is attributed to the lessened physical load in that age group The abnormal electrocardiogram, nevertheless, is an indication of disease and is of prognostic significance

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ROCKY MOUNTAIN SPOTTED FEVER *

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Rocky Mountain Spotted Fever was considered for many years to be a medical curiosity existent only in the Rocky Mountain states and portions of adjacent areas. In 1931 the disease was first proved to be present in other sections of the country, far removed from its supposed locale. Previously, competent physicians from time to time had insisted that they were seeing cases of tick fever in these latter areas, but little credence was given their contentions, it being assumed that they were confusing the disease with typhus fever because of its similar clinical manifestations. The infected individuals, however, were not lice infested, and being for the most part rural residents there was little possibility of overcrowding. In most instances they did give a history of having had ticks attached to their persons at some time preceding the onset of the illness.

At the present time it is generally agreed that tick fever is widespread in distribution. An average of 600 cases are reported in the western endemic area yearly. In addition, it is conjectured that at least 200 additional ones appear each year in the remainder of the country. The figures are conservative for the reason that many cases undoubtedly go unrecognized, being under the care of physicians for the most part unfamiliar with the disease. The average mortality is considered to be approximately 12.5 per cent. A disease which terminates fatally for every eighth individual contracting it demands earnest consideration by our profession.

Tick fever has potentialities for greater dissemination. Ticks are the only known vectors, but there are many species of them, universally distributed throughout the country. Animal hosts, wild or domesticated, are abundant. The disease has been considered as one of rural communities, but has numerous other possibilities. Many people vacation each year in the Rocky Mountain areas, where several of the national playgrounds are located. It is possible for them to pick up ticks. Because of the rapidity of present day transportation and the relatively long incubation period of the disease, infected individuals may return home before showing active manifestations, reporting themselves for care to physicians who have never seen a case of tick fever. Wider knowledge regarding the disease appears essential. For that reason this article is presented, in order to familiarize the reader with a disease which can in time assume proportions of national importance ^{1, 2, 7, 10, 11, 12, 37}

Tick fever is not a disease primarily of human beings, but is one of ani-

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imals and would exist if the former were eliminated from the picture. Ticks are not parasites of the human race. When individuals are bitten the occurrence is purely an accident. The wood tick of the western endemic areas is the vector of the disease in this section of the country. Transmission of tick fever by species other than the wood tick is apparently possible, because with allowance for different life cycles and host habits of other types, maintenance of the disease is explained satisfactorily wherever it exists. At least eight other species of ticks have been incriminated in the transmission of the disease, serving as carriers of the infection in nature or both as carriers and transmitters of it to human beings. The potentialities of the majority of them with the exception of the common dog tick are not perfectly understood. In every region of the country, however, in which the occurrence of tick fever is a possibility native species have been isolated and their characteristics in part at least identified ^{15, 21, -- 23, 27, 29, 30, 35, 38}

Tick fever occurs more frequently in men because they are most often exposed to infection. Neither sex is immune. The disease strikes individuals of all ages. Women are more sensitive to the presence of crawling ticks, often removing them before they become attached. Children ignore their presence, but for some reason appear to be less frequently exposed to infection, and when exposed less often develop tick fever. Persons such as prospectors, sheep and cattle herders, wood choppers, berry pickers, farmers and ranchers, whose occupations place them in contact with infected ticks, show the highest incidence of the disease. Tick fever is prevalent among unprotected laboratory workers, as a result of handling engorged ticks which can easily rupture and so spread their highly infectious contents.

The disease appears to have a cyclic tendency, more cases appearing during some years than others. The reason for this trend is unknown, but it is believed to depend upon local and regional conditions. The number of individuals exposed, the abundance of ticks, the percentage of ticks carrying infection, the capability of the virus to produce frank infections, and the possible relationship between the prevalence of ticks and animal hosts seem to play a part.

The highest incidence of tick fever in the western area is from the early spring into the early summer months. In the mountainous regions it is highest during the late spring months, owing to delay in the advent of warm weather. In the eastern areas the disease is more prevalent in the late spring and the early summer months, but cases can occur in the fall of the year. Dry and warm days activate ticks. Cool and rainy days render them dormant. In any locality tick fever may occur in the colder months of the year, should there be an abundance of warm sunshine or adequate conditions of artificial heat, releasing ticks from their dormant state so that they are reactivated and start to feed.

The virulence of tick fever varies greatly in different localities but appears to remain fairly constant in any one region. Reasons for the variance are not known. It is supposed that repeated passages of the virus through

successive animal hosts play a part. It is justifiable to speak of mild, moderately severe or severe types of the disease, in view of the great differences in virulence of the infection in various localities and sections of the country^{10, 15, 33}

The incubation period of tick fever is usually from four to eight days, the extremes being two to 12 days. The prodromal manifestations are malaise, headache, anorexia and chilly sensations. These vary in degree, lasting two or three days and resembling in many respects the invasion of any common febrile illness.

The onset of the disease is usually abrupt, coming as a rule in the late afternoon or early evening. It is manifested by the occurrence of a definite chill, pronounced frontal headache and severe aches and pains in the muscles, bones and joints. Aches and pains are more pronounced in the back and lower extremities. Movement of the calf muscles or firm pressure over



FIG 1a

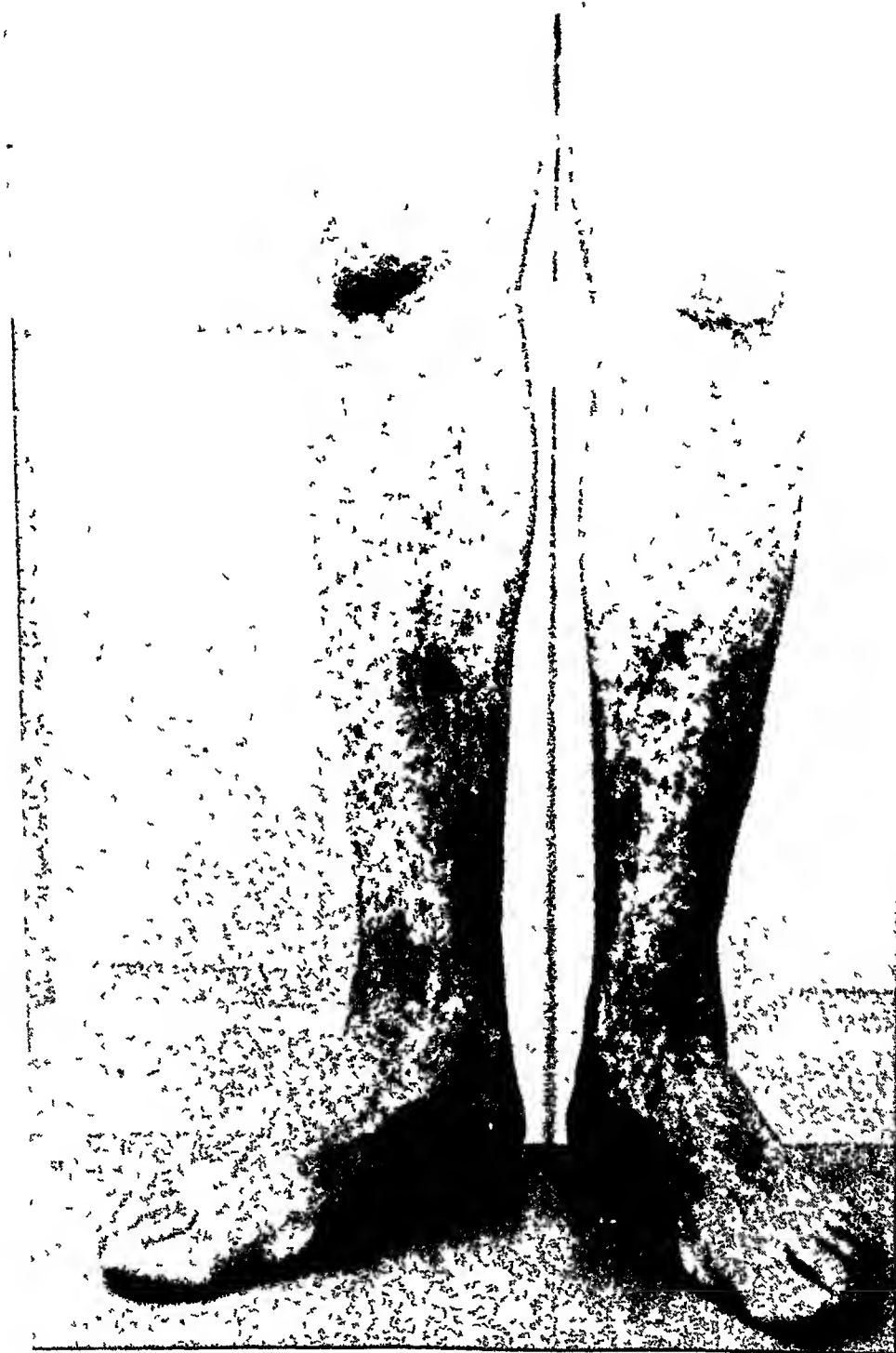


FIG 1 b

Figs 1 a and b Rocky Mountain spotted fever The petechial eruption on the wrists and ankles within a few days of the onset of the disease It has begun to spread over the extremities A site of former tick attachment may be seen on the right shin

them often elicits pain. Inspection of the patient may reveal the presence of attached ticks. Usually, however, none is found, although indurated areas at the sites of former attachment may be palpated. The bite regions show no peculiarities. They may appear discolored from blood extravasation.

The eruption may consist at first of macular rose-colored elevated areas, resembling the exanthem of measles, particularly in fair skinned individuals. The macular eruption is not at all distinctive. It can be nonexistent or passed over unnoticed. The characteristic petechial eruption first appears on the wrists and ankles 24 to 48 hours after the onset of tick fever. It may be missed early in individuals having suntanned extremities from over-exposure to the elements, or in dark skinned races (figure 1). The petechial eruption spreads from its original location on the extremities in a centripetal fashion over the scalp, chest and abdomen, and from there to the remainder of the body. It is always more marked on the extremities than elsewhere. Its extension is complete in two or three days (figure 2), when complete associated generalized aches and pains are somewhat ameliorated. The fever, however, remains unabated. The petechial eruption is considered to be the most characteristic finding in tick fever. However, some cases never show a rash, others die before its appearance from toxemia, and a few are said to have a bizarre eruption. Petechiae are accentuated by tourniquet application. They do not disappear on pressure except during the early stages. Petechiae may eventually come to involve the palms of the hands, soles of the feet and the mucosa of the inner cheeks and throat. A patient with such an eruption is truly speckled or spotted, the eruption covering the entire body. The petechial eruption may appear in successive crops, each one having a life cycle of approximately 14 days.

In milder forms of the disease the eruption tends to remain discrete, being at first rose-red and later bluish red in color. In more severe cases, discreteness does not persist. The petechiae increase in size and become confluent, finally coalescing and then becoming purpuric (figure 3). A mass of purpuric areas may involve the entire body. As a result of terminal gangrene, dependent portions such as the scrotum or soft palate may slough (figure 4).

In cases which go on to recovery the petechial eruption gradually fades. Fading takes much longer in the more severe cases than in mild ones. It occurs with the fall of temperature. Desquamation may follow, either branlike in character or so complete that casts of a part are exfoliated (figure 5). Pigmentation remains where petechiae formerly existed. This may be followed by the formation of minute cicatrices. For months following recovery from tick fever over-exertion or exposure to heat or cold will again bring out a temporary appearance of the eruption.

The temperature rises abruptly within the first 24 hours of the onset of the disease, with but one or two slight remissions, reaching a fastigium of 103° F, to 105° F, by the beginning of the second week in mild cases, by the second or third day in more severe ones. With recovery from the acute

manifestations of the illness it falls either by rapid or slow lysis, rarely by crisis. There may be slight temperature remissions in mild cases, but fever is constant or slightly rising in more severe ones. It may become distinctly remittent after the first few days, particularly in moderately severe protracted cases, but never ceases completely until the terminal lysis. In very severe

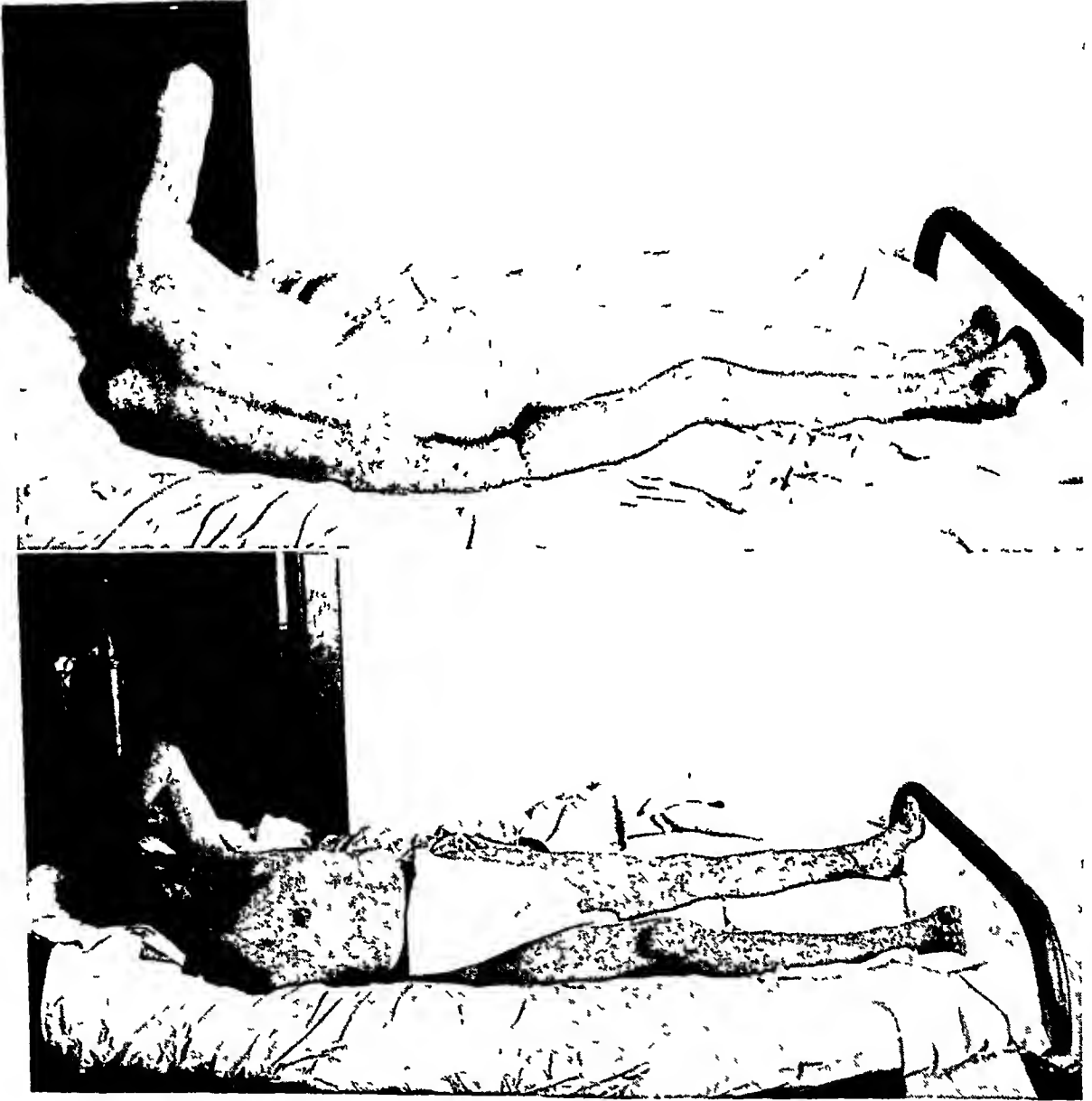


FIG 2 Rocky Mountain spotted fever. The petechial eruption after extension is complete, the first week of the illness. It is most marked on the extremities. The patient is a white man severely suntanned from overexposure to the elements.

forms of the disease, the temperature may be normal from the first or sub-normal, to rise sharply in the 24 hours preceding death, or it may be high from the first, then fall to normal and again rise sharply before death occurs. The temperature can drop to normal, but show a secondary rise if complications ensue.



FIG 3 Rocky Mountain spotted fever The petechial eruption in a severe case during the third week of the disease The lesions are confluent and beginning to coalesce. Purpuric areas are present on the left lateral thigh region



FIG 4 Rocky Mountain spotted fever The petechial eruption in a fatal case during the terminal stages of the illness Purpuric areas are present, there being terminal necrosis of the buttocks



FIG 5a

Early in the disease the pulse is of good volume. It is slow in proportion to the temperature, the rate usually being about 90 beats a minute. Early disproportion of the pulse and temperature ratio is one of the characteristic findings of tick fever at its onset. In severe cases, when myocardial weakening has occurred as a result of toxemia, a loss of strength and



FIG 5 b

FIGS 5 a and b Rocky Mountain spotted fever The petechial eruption during the terminal stages of a fatal case Desquamation has begun, so complete that casts of body parts are extruding An attached wood tick is present on the left lateral neck region

volume of the pulse comes about It rises out of proportion to the temperature The systolic pressure falls and the first heart sound becomes muffled and indistinct

The respirations are at first normal or but slightly increased In severe cases, with alterations of the pulse and temperature ratio, they increase Increase in rate is noted if bronchopneumonia supervenes

Muscular and joint pains in the back and extremities, petechial eruptions, alterations in the pulse and temperature ratio and respiratory variances are the most characteristic findings of tick fever There are other manifestations, more or less typical in nature They exist in various combinations, their intensity often depending upon the severity of the existent disease process

The picture presented by a patient severely ill or even moderately so is that of marked prostration The senses are dulled Individuals are quite apt to appear rational at times, but close observation reveals considerable mental confusion Amnesia is present and may exist until the eruption is complete or for some time afterward Patients appear anxious, with flushed cheeks and injected conjunctivae Photophobia may be present Severe nervous disturbances such as lethargy, restlessness or nervous irritability are often seen, particularly in children, in whom convulsions may develop before death Insomnia is at times troublesome Active delirium can occur, espe-

pecially in severe cases in the terminal stages of the illness. Muscular twitchings are common. There may be fibrillatory tremors. The muscle tonus of the body is definitely increased. Muscular aches and pains are present throughout the disease, at times being excruciating. Abdominal muscular aches can be so intense as to simulate an acute surgical condition in the abdomen. On moving the neck a slight stiffness is often detected.

The tongue is at first swollen and moist. In severe cases it becomes dry, coated, showing a dark red border with prominent papillae. It may be profoundly swollen so that it protrudes from the mouth. Should coma ensue, it becomes fissured and covered with sordes. Pharyngeal engorgement at times exists, accompanied by a dry, hacking nonexudative cough, resulting from bronchial irritation. Profound chilliness is often troublesome. It is not a true shaking, chattering affair, but nevertheless is more persistent and drawn out than in other fevers, often lasting for as long as two to four hours at a time.

The skin is often tender, to the degree that patients complain of pressure from light bed coverings or drafts of air. As the disease progresses, in more severe cases it becomes dark red or bluish in color, particularly on the back and thighs. It is common to see an illdefined bluish discoloration beneath the skin surfaces when the patient is examined under satisfactory light conditions. Severe cases of tick fever develop extensive sloughs of dependent portions of the body such as the scrotum. Necrosis involving the prepuce, fingers, toes or lobes of the ears can occur. Alopecia sometimes appears and may be permanent.

Anorexia often exists. Nausea and vomiting take place in some cases. The vomitus may later contain blood. Diarrhea, with or without bloody stools, occurs occasionally but is unusual. Constipation is the rule, often quite obstinate in its manifestations. Sphincter control may be lost, especially in severe cases. The spleen is enlarged and tender and often the liver also. Jaundice exists in some degree, as noted on inspection of the sclerae. It is nonobstructive in character and deepens markedly during the terminal stages in severe cases.

There may be an inability to void as a result of increased muscle tonus. Incontinence is sometimes seen, particularly in severe cases. Urination may be distinctly painful. At times a lessened secretion of urine occurs, owing to kidney changes or a failing circulation. Total suppression may come about in fatal cases.

The blood findings are for the most part not unusual. There is a lowered red blood cell count and hemoglobin content late in the disease, resulting in a secondary anemia. The total white blood cell count may be as high as 30,000, counts of 12,000 to 15,000 being the average. At times a relative mononucleosis is found, averaging from 10 to 12 per cent.

The urine may be scanty and highly colored, with an increased specific gravity. Some patients, particularly old and debilitated individuals, show albumin in varying amounts, together with acetone bodies and microscopical al-

terations. Such changes are not so manifest in younger persons, or in those who have previously enjoyed good health.^{7, 8, 9, 10, 17, 19, 22, 30, 33, 38, 39, 41, 42, 47}

Numerous laboratory procedures are in use for the diagnosis of tick fever. The Weil-Felix agglutination reaction is perhaps the most popular and widely used at the present time. It is important at least in determining the presence of a rickettsial infection. The significance of the procedure rests on the finding that many tick fever sera, if taken late in the course of the disease or during early convalescence, agglutinate various strains of *Bacillus proteus*. Saline suspensions are added to blood sera taken from suspected cases, and agglutination occurs in many instances of tick fever. However, certain restrictions tend to lessen the usefulness of the procedure. Affinities of the agglutinins of tick fever sera for *Bacillus proteus* strains is broader than those of typhus fever, so that it is not agreed at the present time what strains are most advantageous to use. Negative agglutination with a few strains of the organism might not necessarily indicate that the same would be the case had additional strains been used. Many tick fever sera, even when taken at the most favorable period of the disease, do not bring about agglutination in sufficiently high titer to be significant. Occasionally, apparently normal sera cause agglutination in as high titer as occurs in unquestionable clinical cases of the disease.

The procedure has considerable merit in spite of these faults. Many of the sources of error will undoubtedly be obviated in the future, with additional research on the problem. Agglutination is usually produced in a dilution of 1:160 or more. A titer of 1:10000 may be reached. Agglutination in a titer of 1:160 is considered to be quite significant. Three blood samples should be taken. The first is to be obtained as soon as the nature of the illness is suspected or when the eruption first appears, the second between the tenth and fifteenth days, preferably on the twelfth, and the third during convalescence. In a series such as this, a positive reaction is indicated by increasing titer of the agglutinins, accompanied at times by an increased affinity for *Bacillus proteus* strains. The agglutinin content of sera of patients with tick fever increases as the disease progresses, then gradually subsides as the acute manifestations of the illness recede, thereby indicating a close relationship between the disease process and the reaction. The reaction may be negative at the time the first test is made, but usually by the end of the second week of the illness it is positive. If the second one is negative, that taken during the third week is almost invariably positive.^{4, 8, 9, 17, 20, 25, 34}

Tick fever may be confused with various other infections, particularly when the disease appears unexpectedly in a locality or when encountered by those unfamiliar with its manifestations. The diseases most commonly causing confusion are typhoid fever and allied conditions, severe measles, smallpox, epidemic meningitis especially of the septicemic variety, undulant fever, streptococcus septicemia, purpura, typhus fever and Colorado tick fever. It is not within the scope of this paper to discuss the majority of the conditions. For the most part confusing diseases can be ruled out by careful

histories, examinations, and repeated observations of the infected individuals. Endemic typhus fever and Colorado tick fever, however, are two diseases worthy of discussion.

In the eastern and southern sections of the country endemic typhus fever is obviously often confused with tick fever, for the reason that both diseases are found in the same localities. There is a striking clinical resemblance between the two rickettsial infections, at times making differentiation a most difficult procedure. Endemic typhus fever is transmitted primarily by infected rat fleas, tick fever by infected ticks. Typhus appears for the most part during the late summer and fall, tick fever of the eastern type during the summer and early fall, of the western type in the spring and early summer. Endemic typhus fever is found among food handlers, the infected individuals usually being urban residents. Tick fever occurs for the most part in those having rural contacts. Even though the symptomatology is quite similar in both diseases, the general clinical features are quite intensified in tick fever. The incubation period is shorter, the onset more explosive and severe. The temperature rises more rapidly. Although it recedes in both diseases by lysis, the fall is much slower in tick fever. The petechial eruption appears first on the body in typhus, spreading from there to the extremities. In tick fever the original site and manner of spread are the opposite. In tick fever the eruption tends to be more extensive and cyanotic, being more profuse in distribution. The pulse tends to be higher in proportion to temperature, particularly in severe cases. Nervous and mental symptoms are more profound and delirium is more often encountered, coma preceding a fatal outcome. In tick fever convalescence is more slowly established.

Routine laboratory procedures do not furnish much assistance in differentiating the two diseases, agglutination with *Bacillus proteus* strains tending to be positive at some time during the course of both. In order to establish absolute identification it may be necessary to study the effect of virus on laboratory animals. Observations of the clinical pictures obtained by guinea pig inoculations or typical histological alterations produced in the brains of laboratory animals may be necessary. Cross immunity tests are sometimes used. Their significance depends upon the finding that animals which have recovered from typhus fever remain susceptible to tick fever, and that animals which have recovered from tick fever remain susceptible to typhus fever, but not to further inoculations of tick fever virus.

Colorado tick fever, tick toxemia, mountain fever or American mountain tick fever has a geographic distribution similar to that of tick fever in the western endemic areas. It follows the bites of wood ticks. The disease is a brief, seasonal, nonexanthematous remittent fever, displaying a characteristic symptomatology. There is no known mortality. The onset is sudden, a fastigium of fever being reached within the first 24 hours. Two febrile periods usually occur, each of two to four days' duration, with a remission period of several days between. There is no eruption. Associated symptoms are malaise, chilly sensations, severe occipital headache, non-productive

conjunctivitis, glazed white coating of the tongue, photophobia, and generalized muscular and joint pains with severe aching in the lumbar region. There is no pharyngeal engorgement. Terminal necrosis and gangrene do not occur. The site of a tick bite may become an indolent ulceration. Aches and pains are usually referred to the back and loins, whereas in tick fever they are for the most part in the back and lower extremities. Insomnia is troublesome in tick fever, being either slight or transitory in Colorado tick fever. The pulse has a marked tendency to slowness in the latter. Constipation and urinary retention occur in both diseases. Bronchial irritation does not exist to the degree found in tick fever.

The disease has been reported as a mild form of tick fever. Although the possibility has not been finally excluded, it does not seem likely that such is the case. In light of data available at the present time, it must be assumed that Colorado tick fever is a separate disease entity. Many of its features are as yet obscure and ill-defined. All attempts to reproduce infections in laboratory animals by blood inoculations from those ill with the disease have met with failure. Blood sera from infected individuals do not agglutinate strains of *Bacillus proteus* in suspension.^{7, 8, 10, 22, 28, 31, 32, 36, 37, 40, 42, 43}

Tick fever is a self limited disease, terminating either in recovery within a period of a few weeks, death during the acute phases of the illness from toxemia or in the later stages from complications. Seriously ill patients are said never to recover should complications ensue. The main ones are secondary infection of the spleen and bronchopneumonia, the latter being especially frequent in stout people and alcoholics. Phlebitis is not uncommon. Neuritis or joint pains sometimes appear. They may persist for many weeks following recovery from acute manifestations of the disease. Deafness, visual disturbances, speech slurring and mental confusional states may be noted for various periods of time. Fortunately they are usually transitory.

The ultimate prognosis in tick fever depends upon the ability of the infected individual to withstand the ravages of the disease, particularly as regards renal and myocardial intoxication. Omens of bad prognostic significance are a confluent purpuric eruption with terminal sloughing, marked pulse and temperature reactions, severe intoxication of the brain and central nervous system, or the development of complications in old and debilitated patients or those ill with intercurrent diseases.^{10, 38}

The disease could be eradicated were it possible completely to dispose of the tick vectors. Such an extensive undertaking is naturally impossible. In all localities in which the disease is found, conditions favorable to ticks exist, allowing hosts for both adult and immature forms to flourish in abundance. Vegetation and physical conditions have an indirect influence, inasmuch as they afford suitable surroundings for animals serving as tick hosts. Once ticks are established in a locality, they continue to thrive if there are horses, cattle, sheep or larger wild animals present, together with rodents in the same regions. In the western endemic areas measures have been undertaken to

rid sections of conditions predisposing to perpetuation of the disease. Although some of these have been to some extent successful, they remain for the most part purely experimental, the results being contradictory and inconclusive.

Casual travelers may prevent exposure to infection by remaining out of tick infested localities. Such precautions are not at all times feasible. Individuals may wander into hazardous areas, not realizing the dangers which they incur, or business activities may necessitate their presence in a region in which tick fever is known to originate.

Inasmuch as ticks are usually found on low grass or other vegetation not over 18 inches above the surface of the ground, trousers worn should be gathered in such a manner as to prevent them crawling up the legs. Ticks do not jump on those who pass their vantage points. Instead, they lie in wait hunting for victims, actively moving their numerous serrated legs by which they transfer themselves to objects which brush by. All clothing worn should have a minimum of openings in order to prevent ingress to the body surfaces. Smooth clothes prevent ticks from gaining footholds, yet those with a rough nap impede their progress once they have gotten on the body covering. While in tick infested localities it is a good plan occasionally to pass the hand over the back of the neck in order to detect the presence of crawling ticks. It appears that they often gain entrance to the body surfaces in this vicinity.

Clothing should be completely removed at least two or three times a day and the body thoroughly examined for the presence of crawling or attached ticks. Body folds, crevices and hairy portions must not be missed, for the reason that ticks often hide away in regions in which they are free from rubbing and cannot easily be removed manually. Camps are to be located in regions in which rodents are at a minimum, preferably in locations in which no low grass, sagebrush or small bushes are growing. Wooded areas along creek banks or the vicinities of old trails and roads are best avoided as excellent tick habitats. The best camping places are considered to be those in which standing timber is present, with a minimum of low vegetation. Before retiring for the night those in the open must again carefully inspect their persons, clothing and bedding. After returning from trips the latter should again be thoroughly gone over, aired and removed to buildings not used for human habitation. When ticks have taken up their abode in any location, eradication is a most difficult procedure.

Once on the surface of the body ticks do not immediately attach themselves, but move slowly about for a variable length of time, during which they seek a suitable location. It is supposed that they are not actively infectious for a period of several hours after attachment has occurred, but little reliance can be placed on this contention. When found, attached ticks must be removed without delay. The procedure is often one requiring considerable skill and perseverance. As a rule only the head of the tick is found embedded beneath the skin surface, the body remaining free and protruding at

an angle from it. The head is held firmly in place by means of mouth parts, so that hasty or careless plucking can serve to remove the body alone, leaving the remainder which serves as a source of infection. Gentle traction may be successful. Close inspection then reveals the tick to be intact, often with a small fragment of epidermis caught in the mouth parts. Should the procedure fail, a small fragment of skin in which the tick's head lies embedded can be elevated with a pair of tweezers and a wedge of tissue snipped with a fine pair of scissors. The maneuver insures complete removal. The resultant wound from tick extraction is to be thoroughly cauterized, using phenol, silver nitrate, iodine or similar agents. A light dressing can then be applied. When ticks are accidentally crushed on removal, the discharged contents must be thoroughly removed from the hands by soap and water. They are apt to be highly infectious, being known to penetrate even un-abraded skin surfaces.

Tick fever vaccine gives protection against the disease. It should be received by all individuals whose activities either for the purpose of business or pleasure take them into tick infested localities in which the infection is known to exist. The material is prepared by The Rocky Mountain Spotted Fever Laboratories of The United States Public Health Service at Hamilton, Montana. Recommended dosage for adults is two cubic centimeters, repeated at an interval of from seven to 10 days. If the particular locality is one in which serious cases of tick fever are known to originate, the second injection must be followed by a third, administered after the same time interval. Children receive a proportionate amount of vaccine, one cubic centimeter being recommended for those 10 years of age or younger.

The degree of protection afforded by vaccine and the duration of such protection varies with vaccinated individuals and the virulence of the infection to which they are exposed. As a rule, those vaccinated in the spring of the year retain a considerable degree of immunity for at least the remainder of that year. This is usually sufficient to afford full protection against the relatively mild strains of the disease, but is progressively less effective as the virulence of the virus is increased. Nevertheless, against even the more severe forms of tick fever it is usually adequate markedly to ameliorate the usual stormy course of the infection, so as to insure ultimate recovery. Complete protection of occasional persons is not unlikely.

If individuals are infected during the vaccination period, there is a strong possibility that the subsequent course of the disease will be favorably affected, even in cases of high severity. Vaccinated cases which develop tick fever show less intoxication, less damage to the heart and kidneys and a more discrete, brighter colored rash which does not tend to become hemorrhagic. The rash is more sparse in character, there are less mental depression, insomnia and milder nervous symptoms. In fact, the clinical picture in all respects is less alarming. Convalescence is usually more rapidly established and is of shorter duration.

In areas in which relatively mild infections prevail and the incubation period of tick fever is prolonged, administration of vaccine as soon after exposure as expedient may ameliorate impending infections. This appears possible, particularly in those individuals who have been vaccinated during preceding years. The administration of vaccine after exposure to infection in areas in which the disease is known to show marked severity is not recommended, unless the individuals have been vaccinated previously. Nevertheless, many physicians resort to the procedure irrespective of the locality from which exposure occurs, seemingly with beneficial results in the majority of cases.

It is probable that a certain proportion of individuals carry an indefinite degree of immunity over into the second year, even against highly virulent strains of virus. The degree of protection appears to be greater in those who have been vaccinated for two or more successive years. Evidence does not indicate that any considerable degree is carried into the third year. In order to afford the greatest degree of protection possible, it is recommended that immunization be performed each year.

Intramuscular administration of vaccine is not known to bring about more than a slight constitutional reaction. However, the same precautions must be observed as with the injection of any biological product intended for an immunization procedure. Immediately there ensues a sensation of fullness at the site, followed by one of smarting or stinging. Itching may occur, exacerbated by scratching or rubbing the part. A generalized malaise sometimes occurs, often with a slight febrile reaction. The manifestations are usually transitory, subsiding before subsequent administrations of the material. These usually result in much milder manifestations or none at all. Reactions to the use of vaccine have not been so prevalent in recent years, particularly since the utilization of the chick tissue preparations^{4, 5, 13, 14, 15, 24, 26, 38, 44}

At the present time treatment of tick fever is recognized to be purely symptomatic and supportive in character. There is no recognized specific. Even though none exists, its absence should not predispose to an attitude of helplessness and hopeless inactivity on the part of attending physicians. Carefully directed symptomatic care and supportive measures aid patients to eliminate toxins from their bodies, support them during the period of invasion and assist them in every other means possible. Vigorous yet well directed procedures bring about a successful outcome in many patients who appear essentially hopeless as regards recovery at the time first seen.

Bed rest is enforced from the onset of the illness, in order to conserve strength as much as possible. It is important that patients be kept as quiet as possible both mentally and physically by such measures as baths, packs and the use of simple sedation. If necessary, codein or morphine may be resorted to. Bath temperatures must be 70° or above, cold or tepid bathing often resulting in shock to seriously ill patients.

The gastrointestinal tract must be carefully watched. Mild enemas or catharsis are permissible in order to facilitate regular elimination. The diet should be nourishing, adequate and easily digestible. Frequent urinary examinations are indicated so as to detect pathological alterations at their onset. Fluids must be freely administered, by mouth if tolerated. If vomiting is severe, they may be given by other routes. Adequate amounts of fluids have a definite beneficial effect on the ever present trend to acidosis.

It may be necessary to support the heart should myocardial weakening appear imminent. Local treatment to the skin is important. Equal parts of witch hazel and alcohol in water applied once or twice a day as a sponge often comforts and invigorates severely ill patients. It removes soreness from muscles and revives them. As a result, patients are less mentally dulled, appearing stronger for several hours following the procedure. Mouth hygiene is extremely important. Oral antiseptic washes serve to rid the region of accumulated waste products, so that the sufferers are made more comfortable during the serious phases of their illness.

Convalescent sera and transfusions have been resorted to, apparently without beneficial effect. Autohemotherapy has been used by some physicians. Ten to 20 cubic centimeters of citrated blood are readministered intramuscularly, the procedure being repeated as often as necessary during the acute phases of the illness. Many drugs have from time to time been lauded as specifics in the treatment of tick fever. It is generally agreed that the action of the majority of them is not certain, and for that reason they have been discarded for the most part. As might be expected, the sulfonamide drugs have been tried. Definite information regarding their efficacy is still lacking, but from that existent it is believed they have little or no value in the therapeutic management of tick fever. Tick vaccine should never be used for the purpose of treatment. It is felt that it has no beneficial action when used for this purpose. In milder cases its use is too drastic to be justified, in more severe ones it may prove very dangerous as regards ultimate recovery.^{3, 5, 13, 15, 16, 18, 19, 20, 23, 28}

In foregoing paragraphs the writer has attempted to present as accurate a clinical picture as is possible of tick fever as we understand it at the present time. There are, however, additional features in respect to the condition which the reader may find of some interest.

Practicing medicine in the western endemic area, in a section of Wyoming in which the disease appears with considerable frequency, he has had occasion to make an extensive study of its various aspects. Almost without exception the cases seen have ranged from moderately severe to severe in intensity. Seldom has one of mild intensity been noted.

Intravenous administration of neosalvarsan dissolved in an aqueous solution of metaphen has been used in the treatment of rickettsial infections. In endemic typhus fever their use has been reported to have met with considerable success. Inasmuch as tick fever has a striking clinical resemblance to endemic typhus fever, it was decided in 1934 that the two drugs should be

given a fair and thorough trial in order to determine whether or not they would prove efficacious in treatment of the disease

That year the first and original investigations on the use of the material were undertaken by the late Dr J C Kamp and the writer. The year 1934 proved to be one of high seasonal incidence, a total of nine moderately severe cases of tick fever being under our immediate care. All of the patients received neosalvarsan dissolved in metaphen solution. None of them terminated fatally. In no case had vaccine been received for the purpose of immunization against the disease. Owing to the favorable responses received it was decided that in the future the drugs would be administered as a routine measure in all cases of tick fever which came under our supervision.

Since that time an average of three to four cases of the disease have been under care each season. During the past eight years all cases so treated have recovered. Observation of the individuals has shown less evidence of intoxication, minimal damage to the heart and kidneys, and a more discrete, brighter colored rash which does not tend to become hemorrhagic. The rash has been more sparse in distribution. Less mental depression is apparent. There have been milder nervous symptoms. In fact, the clinical picture has been in all respects less alarming. Convalescence has been more rapidly established, being of shorter duration with a minimum of complications. As a result of thorough and conscientious clinical trial the writer has been convinced that the material is a definite therapeutic aid in the treatment of tick fever.

Use of the two drugs in combination is thought in no way to exert a specific action on the manifestations of the disease. Admittedly their approach is indefinite. It is felt, however, that the effect should be credited to a direct action of the drugs on rickettsiae in the tissues of infected individuals. It may be attributable to a combination of the bactericidal action of metaphen together with the spirocheticidal action of neosalvarsan upon a microorganism which is bacterium-like in character, yet has staining properties similar at least to those displayed by spirochetes.

In the performance of the procedure, 0.3 gram of neosalvarsan is dissolved thoroughly in 10 cubic centimeters of an aqueous solution of metaphen. The resultant mixture is yellow and turbid, its appearance changing but little on standing. It is warmed and injected slowly by vein, the same precautions being observed as with any chemotherapeutic agent intended for intravenous administration. Solution is administered and blood withdrawn alternately into the syringe until the entire amount has been given. The procedure usually consumes a period of five to 10 minutes. No reactions, local or constitutional, either immediate or delayed, have thus far been noted.

It has been routine for the writer to repeat the administration of the two drugs at three to four day intervals. Customarily three or four injections have been sufficient to ameliorate the clinical picture so as to insure ultimate recovery. Continued or recurrent manifestations would apparently justify additional administration of neosalvarsan in metaphen solution.

The writer has customarily secured first morning specimens of urine for examination on the days the material is administered. He has not to the present detected grave enough indications of kidney injury to prohibit use of the drugs. However, a word of warning appears indicated to those who might contemplate their use in the treatment of tick fever. Should a case of the disease demonstrate severe renal injury as a result of the infection, careful consideration must then be given to the question as to whether or not their use is justified. The inherent risks associated with the use of drugs of considerable potency on an already damaged kidney must be weighed against benefits to be derived from their administration.

It is not possible for the writer to present a detailed discussion in this article of the several cases of tick fever which have come under his supervision. However, one such case has been selected for presentation, typical in the majority of its aspects of those with which he is familiar.

CASE REPORT

Mr H S, aged 35, a shepherd, was first seen on May 17, 1936, complaining of generalized body aches and pains, most prevalent in the larger joints, back region and extremities, together with recurrent chills and a persistent, severe headache. The patient had felt perfectly well until five days previously, when he noticed increasing tiredness and fatigue. He had worked under inclement weather conditions during the lambing season, for long periods of time having no opportunity to change his clothes or bathe. There had been numerous wood ticks on his person, both crawling and attached, the latter being carelessly removed without further precautions. The same procedure had been customary for many seasons past, there being no apparent ill effects from the practice. The patient had never received tick fever vaccine. The evening before being seen he had undressed, however, and had noticed for the first time a spotted rash on the wrists and ankles. This, together with the general manifestations, caused him to seek medical supervision for his illness. The patient was found to be quite ill, with a flushed face and injection of the eyes. The throat appeared reddened, and there was some cough. The temperature was 103.4° F, pulse 96, and respirations 28. He did not appear completely rational, a rather evident degree of mental confusion being present. There were no other findings save the presence of a petechial rose red eruption, limited to the wrists and ankles, but beginning to spread to the hands, lower arms, feet and lower legs. The patient complained bitterly of generalized muscular aches and pains, most marked in the back and lower extremities. All in all his general condition was one indicating the necessity for immediate hospitalization. No attached or crawling ticks were detected.

Blood count showed 4,000,000 red blood cells, 85 per cent hemoglobin, 6,300 white blood cells, with 67 per cent polymorphonuclears, 13 lymphocytes, 19 monocytes, 1 basophile, 1 eosinophile. A urinalysis showed no sugar, acetone bodies, albumin or microscopical alterations. The blood Wassermann and Kahn reactions were negative.

Diagnosis Early Rocky Mountain spotted fever, moderately severe in type.

Clinical Course The patient was placed at absolute bed rest, with complete mental and physical quiet. A soft high-carbohydrate diet was administered, together with large quantities of well sweetened fruit juices. Medication prescribed consisted of quinine sulfate grains 5, acetylsalicylic acid grains 5, with codein sulfate grains ½, administered at intervals of four to five hours, as necessary. The patient was observed frequently by the writer and was placed in the care of a nurse thoroughly familiar with the manifestations of tick fever. The morning following admission

to the hospital 0.3 gram of neosalvarsan was administered in 10 cubic centimeters of an aqueous solution of metaphen intravenously, on a fasting stomach, a preliminary urinalysis revealing no albumin or microscopical alterations. By May 20, three days after admittance to the hospital, the petechial eruption was complete over the body, having spread in a centripetal fashion from its original sites. A Weil-Felix agglutination test revealed four plus agglutination with proteus OX19F and 504 strains, in serum dilutions of 1:640 and above. An accompanying note from The Rocky Mountain Spotted Fever Laboratories, Hamilton, Montana, stated that the blood serum gave a good positive test for tick fever, the agglutination titer being very high for an early test, in fact higher than is usual in a considerable portion of cases. The temperature remained constantly in the vicinity of 102° F, pulse 100, and respirations 24. The petechial eruption remained discrete in character, but had begun to assume a bluish red appearance. All care was continued and on May 22 the neosalvarsan in metaphen solution was repeated, and again repeated on May 24. By May 27 the petechial eruption had begun to fade, there being a coexistent fall of temperature to normal by rapid lysis. The patient began to appear improved. The mentality cleared, body aches and pains were lessened. The neosalvarsan in metaphen solution was repeated on May 28. On May 31 the Weil-Felix agglutination test was repeated. It showed a four to a two plus agglutination with the same strains of *Bacillus proteus*, in dilution up to 1:10240. An accompanying note stated that the blood serum gave a very strong positive test for tick fever, the agglutination titer being exceptionally high. All medication was discontinued after May 31, the patient being placed on a full diet and allowed up in a chair for increasing periods of time. On June 2 the petechial eruption had almost completely faded. He was allowed up and about, to be discharged from the hospital on June 3, 1936, 18 days after admission. Convalescence was uneventful, there being no complications or sequelae. Recovery was in time complete, the patient returning to his usual occupational duties two months after leaving the hospital.

SUMMARY AND CONCLUSIONS

Rocky Mountain spotted fever is a disease of serious possibilities. It is rather widespread in distribution throughout the country, and has potentialities for greater dissemination. The clinical picture is fairly typical, but there is possibility for confusion with other diseases. Prevention of infection may be secured by simple precautions and by the use of tick fever vaccine. Treatment is symptomatic and supportive. Extensive clinical experience over a period of the past eight years with the use of neosalvarsan dissolved in aqueous metaphen solution, administered intravenously during the acute phases of moderately severe cases, has given to the writer cause to believe that the two drugs in combination exert a definite beneficial action on the course of the disease.

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PORTAL SYSTEM THROMBOSIS OCCURRING IN PORTAL HYPERTENSION *

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PORTAL thrombosis occurs with sufficient frequency in those conditions producing the syndrome of portal hypertension to merit greater consideration than the occasional mention it is accorded. Our past knowledge concerning this interesting condition has been altered considerably by reason of advances in the studies of portal hypertension and its etiological factors. Although portal vein thrombosis is far from common in cirrhosis of the liver, this disease is its most frequent cause. Numerous other conditions which are to be discussed may produce this clinical syndrome. The first complete clinical description of this condition was made by Langdon-Brown¹ in 1901. However, he failed to differentiate between the infective and the bland or aseptic types. Ten cases of aseptic thrombosis occurring in portal hypertension are reported below, nine verified by autopsy and one by operation.

Incidence The general frequency of aseptic portal thrombosis is about 0.1 per cent of all autopsies. Weir and Beaver² found 74 examples of aseptic thrombosis out of 127 cases of all types of thrombosis, and of these, 10 were associated with splenic anemia. Palette³ found eight cases out of 5600 autopsies in four years at the Los Angeles County General Hospital. This disease was recorded in only 21 of 6050 autopsies at Johns Hopkins Hospital⁴. The largest number (seven cases or 2.6 per cent) was associated with cirrhosis of the liver, six with carcinoma, and two cases had cholangitis. Bulmer⁵ reported 67 deaths from gastrointestinal hemorrhage, nine of which were caused by atrophic cirrhosis or portal thrombosis. The condition is encountered more often in men than in women, corresponding with the greater frequency of hepatic cirrhosis among men. In Rolleston's series⁶ of 62 cases of portal vein thrombosis, cirrhosis of the liver was present in 18 of the 38 males and in only four of the females. Langdon-Brown¹ found the portal vein involved in 3 per cent of the cases of atrophic cirrhosis. Portal vein thrombosis was associated with swollen periportal lymph glands (46 per cent), abscess of spleen (28 per cent), carcinoma of pancreas (24 per cent), and primary carcinoma of the liver (11 per cent).⁷ Among 184 cases at the Mayo Clinic there were 17 deaths, three of which were caused by portal thrombosis.⁸

In limiting ourselves to a discussion of the causative factors of portal thrombosis occurring in the syndrome of portal hypertension, and for the sake of etiologic differentiation, the other causes not immediately or directly associated with this syndrome must be mentioned. These are (1) extension of inflammations from neighboring structures (choledochitis, pancreatitis,

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subphrenic abscess, hepatitis, suppurative mesenteric lymphadenitis, chronic peritonitis, cholelithiasis with cholangitis (13 per cent),⁷ inflammation, abscess, and infarction of the spleen, appendicitis), (2) adhesions or localized abscess secondary to peptic ulcer, (3) primary portal vein disease⁹ (chronic phleboscrosis—35 per cent¹⁰ and syphilitic pylephlebitis—10 per cent⁷), (4) adenoma of the liver, (5) intra-abdominal malignancy—46 per cent⁷ (by direct extension or compression), (6) traction or pressure on the portal vein (adhesions, cholelithiasis, chronic pancreatitis and carcinomata), (7) trauma (volvulus injury, kinking of mesentery), (8) infections (pneumonia, infective endocarditis, syphilis,¹¹ etc), (9) myocardial insufficiency^{2,12} (slow circulation), (10) splenic anemia, (11) blood dyscrasias (polycythemia, leukemias, purpura hemorrhagica, and post-splenectomy thrombocytopenia), (12) chemical factors (e g, acute alcoholism^{3,13}), (13) nervous factors (strain and fatigue^{14,15}), and (14) miscellaneous causes¹⁴ (heredity, climate, seasons, endocrines, gastrointestinal allergy, and over-distended stomach¹⁶)

CASES

Only those cases of portal hypertension syndrome with portal venous system thrombosis verified by autopsy examination or operation are presented. They occurred at the Kings County Hospital from 1934 to 1940. Of the 10 cases, nine were males. The ages ranged from 41 to 72, with an average age of 57. The duration of the immediate illness varied from one day to one year, half of the cases presenting complaints for less than one week before admission. The spleen was enlarged in all but three of the cases (70 per cent). The spleen could be palpated in only one patient (10 per cent) who suffered from Banti's syndrome. The splenic weights ranged from 125 to 540 grams. The liver presented cirrhotic changes of varying degrees in all of the cases (100 per cent). It was definitely palpable in four cases (40 per cent), and varied in weight from 920 to 2700 grams. It was definitely increased in weight in four cases (40 per cent). The abdominal fluid was bloody on two occasions (20 per cent) and purulent once (10 per cent). Only one case presented no evidence of ascites (10 per cent). Abdominal pain appeared in varying intensity and location (80 per cent), toxemia (60 per cent), jaundice (60 per cent), gastrointestinal bleeding (40 per cent), intestinal obstruction (30 per cent), constipation (30 per cent), and diarrhea (20 per cent).

In all cases of portal hypertension with portal system thrombosis, cirrhotic changes were found in the liver to varying degrees, and were usually advanced. Associated pathologic lesions included cholelithiasis three times (30 per cent), primary carcinoma of the liver twice (20 per cent), and once each of Banti's syndrome (10 per cent), adenocarcinoma of tail of pancreas, non-specific granuloma of the gall-bladder, and heart disease. Terminal bronchopneumonia occurred in four cases (40 per cent). Associated venous

thrombosis existed in five cases (50 per cent) Pulmonary vessel occlusion (embolism and thrombosis) was present in two cases (20 per cent)

These cases would seem to fall into four anatomic groups: (1) portal vein thrombosis in portal hypertension due to portal cirrhosis, (2) superior mesenteric vein thrombosis, with intestinal symptoms predominating, (3) involvement of the smaller radicles of the portal system (esophageal and gastric plexi, and splenic branches), and (4) portal system thrombosis associated with carcinoma

The following three cases represent instances of portal vein thrombosis in portal hypertension due to portal cirrhosis

CASE REPORTS

Case 1 E M, a 72-year-old white machinist, presented a history of progressive abdominal enlargement for 15 days, accompanied by right upper quadrant tearing pain There were eructations and progressive weakness Past history was non-contributory except for chronic alcoholism

Physical examination revealed the liver two fingers below the costal margin with tenderness in the right upper quadrant The abdomen was distended with fluid The spleen was not palpable The clinical findings were believed to be due to arteriosclerotic heart disease, although the patient was digitalized, he died two weeks after admission Laboratory findings were negative except for a blood urea of 95.3 mg. per 100 c c of blood Creatinine was 1.2 mg

Autopsy disclosed a circumscribed, soft, friable, greenish-brown thrombus in the portal vein which almost completely occluded the entire lumen It could be traced into the liver substance The liver presented a typical atrophic cirrhosis, weighing 920 grams There was evidence of cholelithiasis and terminal pneumonia Ascites amounted to 1000 c c of clear yellow fluid Except for slight coronary sclerosis and myocardial fibrosis, the heart was negative

This case is a typical instance of portal vein thrombosis occurring with the portal hypertension due to typical atrophic cirrhosis Because of the asymptomatic portal cirrhosis, the cause of the acute symptoms was missed clinically

Case 2 A M, white male, aged 63, was admitted with a complaint of increasing abdominal enlargement for three weeks, accompanied by nausea and vomiting after food There was no hematemesis, but he complained of anorexia and chronic constipation Loss of weight was estimated at 80 pounds in four weeks The patient admitted consuming large quantities of alcohol over a period of many years, but past history was negative otherwise

Physical examination revealed a moderately icteric skin The abdomen was markedly distended by ascites, and the liver edge, which was nodular, extended three fingers below the costal margin

Laboratory tests disclosed an icteric index of 120 units, and the serum bilirubin was 16 mg per 100 c c of blood The van den Bergh reaction was direct immediate positive Six days following an abdominal paracentesis of 3800 c c of dark abdominal fluid, jaundice deepened and the patient died

At autopsy, the liver, which weighed 2700 grams, was typical of portal cirrhosis, and the hepatic ducts were dilated by a light cloudy liquid The gall-bladder was markedly enlarged to the size of a small grapefruit, with an irregular gray, nodular lining, and showed evidence microscopically of an extensive non-specific granuloma

In addition to the portal cirrhosis, there was evidence microscopically of obstructive biliary cirrhosis. Marked ascites was present. The portal vein was opened, and at its junction with the liver a few small yellowish projections due to pressure from without were seen. A nodular mass was noted in one of the large branches. Sections were not made, but it is possible that this was a phlebosclerotic patch with a healed superimposed thrombus. In addition, there were ruptured esophageal varices. There was no evidence of malignancy microscopically.

This case is another typical portal cirrhosis producing definite evidences of portal hypertension. It is highly doubtful whether the non-specific granuloma played any rôle in the thrombus formation. The yellow projections may very well have been phlebosclerotic changes. Welch^{17, 18} has pointed out the importance of calcification in portal thrombosis.

Case 3 J L, a Chinese male aged 65, complained of pain in the right upper abdomen of one day's duration. Language difficulty precluded a complete history, but it was ascertainable that he had had a cholecystectomy two months previously and that there had been a "water" discharge from the wound ever since.

Physical examination revealed a biliary fistula with resistance to palpation at the operative site, but no masses. The stools were very light brown and were negative for occult blood. The icteric index was 12.5 units. The van den Bergh reaction was direct delayed faint trace. Urine disclosed many clumps of pus cells and occasional olive casts. The white blood cell count was 14,250, with 71 per cent polymorphonuclears, 18 per cent small lymphocytes and six transitionals. Clotting time was seven minutes, bleeding time three minutes, 45 seconds. Temperature was normal throughout his stay. Beck's paste was introduced into the biliary fistula which roentgen-rays demonstrated in the fistulous tract, cystic, hepatic and common ducts. Drainage from the sinus became blocked. The patient got rapidly worse despite supportive measures, dying one month after admission.

Autopsy revealed no free abdominal fluid. The liver presented portal cirrhosis with superimposed chronic hepatitis and focal abscesses. It weighed 1000 grams. The fistulous tract was filled with Beck's paste. At the ampulla was a large stone, about one-half inch in diameter, which occluded the common duct completely and dilated the entire biliary tract. In the superior mesenteric vein was a completely occlusive fresh thrombus producing gangrene of the distal portion of the ileum. The superior mesenteric artery was patent throughout.

In addition to cirrhosis, this patient had an obstructive process in his biliary tract which precipitated the superimposed hepatitis and focal necrosis of the liver. This infection may have been an added factor which resulted in the thrombosis of the mesenteric vein. Liver infection may cause infection of the portal vein either directly or indirectly by infecting the bile ducts first, the process extending into the intrahepatic radicles of the portal vein.

Three cases of superior mesenteric vein thrombosis with intestinal symptoms predominating are presented, one of which recovered.

Case 4 J M, white male of Irish descent, aged 55, was treated for decompensated arteriosclerotic heart disease six months prior to his present admission. He had been taking digitalis and was well until the ankles began to swell. Other complaints were fatigue, dyspnea and orthopnea. He was referred to the hospital because of liver enlargement. His complaints included right loin pain with small urinary output and progressive abdominal enlargement which had been present for one week. He admitted consuming large amounts of beer throughout his life.

The positive physical findings were bilateral basal râles, blood pressure 150 mm systolic and 86 mm diastolic, cardiac apex at the midclavicular line with regular and occasional premature contractions. The sounds were of poor quality and there was a systolic blow over the aortic area. Because of the ascites no abdominal organs were palpable. There was bilateral pleural effusion, and sacral and leg edema. The clinical diagnosis was decompensated arteriosclerotic heart disease, and cirrhosis of the liver.

Laboratory findings were non-contributory. Three days following a slow paracentesis of 7900 c.c. clear straw-colored fluid, the patient complained of weakness and finally died.

Autopsy revealed the presence of an acute generalized suppurative peritonitis with a fibrino-purulent exudate present over all the abdominal surfaces. A postmortem examination disclosed streptococci and staphylococci. The liver weighed 1400 grams and showed evidences of an advanced portal cirrhosis. The spleen weighed 240 grams. The gall-bladder contained numerous irregular greenish-black stones measuring 1 mm in diameter. A few were found in the cystic duct but the other ducts were unobstructed. The superior mesenteric vein at its junction with the splenic vein revealed an adherent grayish-white and red thrombus attached to the interior of the wall. A similar thrombus was present for one inch at the origin of the portal vein. These thrombi did not completely occlude the vessels and showed areas of necrosis with degenerating polymorphonuclear leukocytes and debris, vacuolization of the media, and intimal round cell collections. The lower esophagus showed the presence of large venous varicosities in which small thrombi were seen microscopically. In addition, the clinical diagnosis of arteriosclerotic heart disease was corroborated.

Besides the definite evidences of portal hypertension due to atrophic cirrhosis of the liver (esophageal varices, ascites, splenomegaly) as the cause of the portal system thromboses, two other factors must be considered. The arteriosclerotic and hypertensive heart disease produced an element of slowing of the circulation with a passive hyperemia of the liver and splanchnic area. Infarction of the small intestine occurred secondarily to a thrombosis and is significant as the cause of death.

Case 5 J. D., white mechanic, aged 42, was admitted with complaints of lower abdominal soreness for five days and vomiting four times the day before admission. There was no nausea, abdominal distention, bowel irregularities, or anorexia. Past history was non-contributory.

Physical examination revealed only slight tenderness in both lower quadrants with rebound tenderness in the lower right quadrant on deep pressure. The abdomen was markedly tympanitic. Sigmoidoscopy presented a reddened mucosa four inches above the sphincter. A flat plate disclosed increased abdominal density compatible with effusion and moderate distention of the proximal half of the colon. The white blood cell count, differential, and urinalysis were all negative despite a low grade fever ranging from 100° to 101° F. The patient left the hospital against advice following moderate improvement with high colonic irrigations, but was readmitted in three days with cramp-like lower abdominal discomfort. His last bowel movement was the day before admission. On examination his abdomen was greatly distended, tense, with tenderness in both lower quadrants. There was a suggestion of fluid wave. The following day he presented hyperperistalsis in the left lower quadrant, and bright blood appeared in the stool.

A flat abdominal plate corroborated the existence of an abdominal effusion with a moderate amount of gas in the large and small bowel, but showed no evidence of obstruction. The white blood cell count was 12,000 with 90 per cent polymorphonuclear

leukocytes The surgical service believed that the condition was intestinal obstruction due to sigmoid malignancy or abscess secondary to a sigmoid diverticulum but postponed immediate operation in view of the very poor condition A transfusion of 550 c c blood was given and two high colonic irrigations of 10 gallons each were administered There was a marked return of stool and flatus However, the patient failed to improve and died 18 days after the onset of the illness, with no attempt at operation

Autopsy revealed the presence of five liters of clear straw-colored ascitic fluid At the junction of the jejunum and ileum were 10 inches of infarcted bowel In the superior mesenteric vein (figure 1) just behind the pancreas, was a completely occlu-

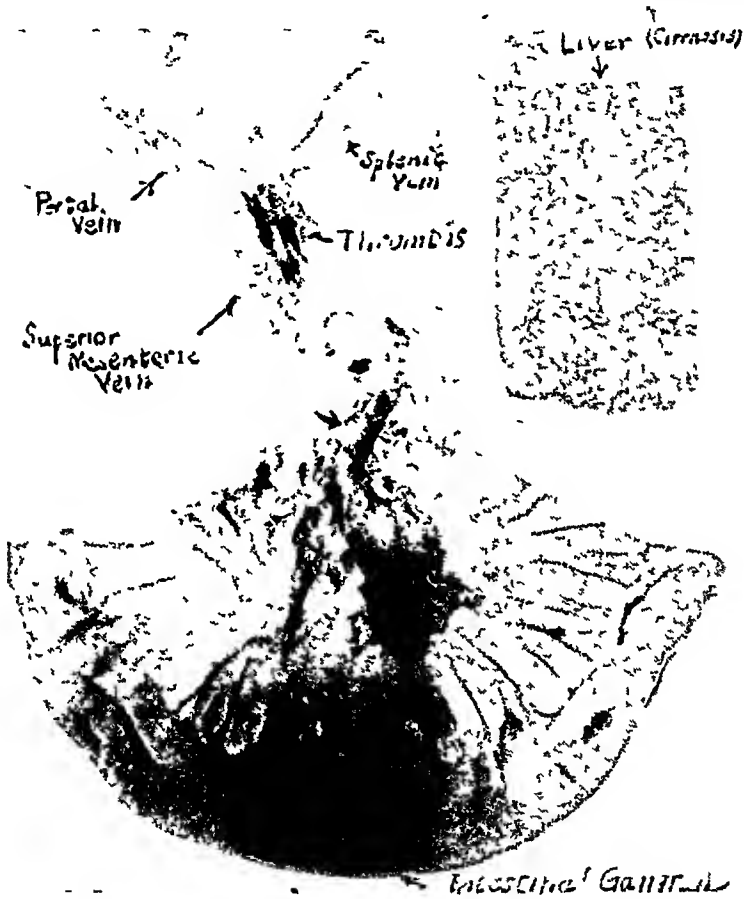


FIG 1 (a) Atrophic cirrhosis of liver with typical thrombosis of the superior mesenteric vein and intestinal gangrene occurring in Case 5

sive fresh red thrombus Some of the veins in the adjacent areas of small intestine were also thrombosed, although these regions were not infarcted The iliac veins and the small veins of the mesentery showed the presence of organizing thrombi The arteries were negative The liver presented marked portal cirrhosis It weighed 1310 grams, the spleen 450 grams There was no evidence of a collateral circulation, although other evidences of portal hypertension were present (splenomegaly and ascites) There was a terminal bilateral bronchopneumonia

This case was typical of portal system (superior mesenteric vein) thrombosis secondary to the portal hypertension induced by a marked portal cirrhosis

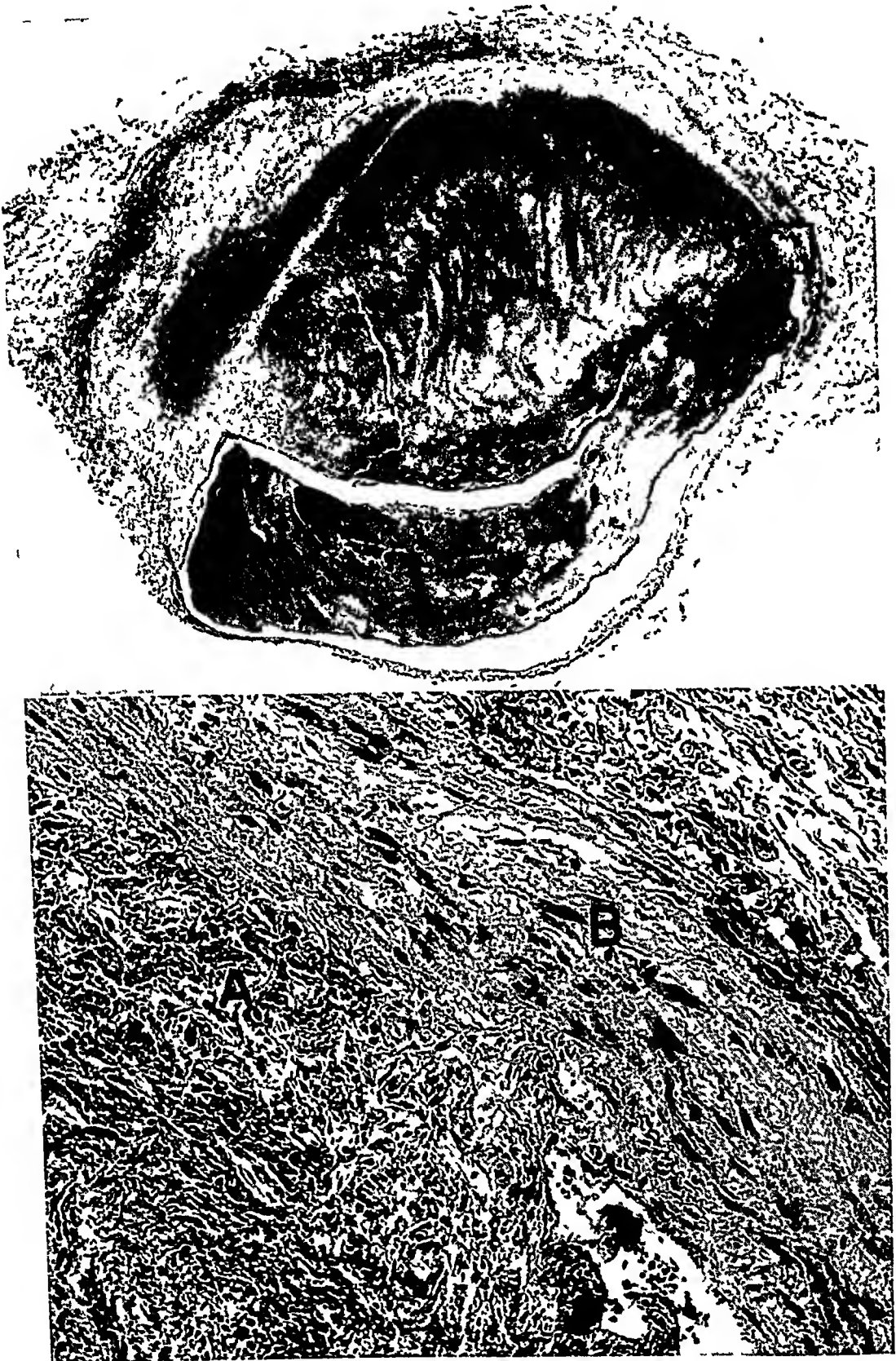


FIG 1 (b) (*Above*) Section illustrating the organizing thrombus with thickening and sclerosis of the wall ($\times 11$) (*Below*) Higher magnification ($\times 150$) of square at attachment of clot demonstrating A thrombus and B changes of vein wall.

Case 6 M W, white male, aged 41, complained of cramping abdominal pain immediately after eating. He could avoid the cramps by eating only tea and crackers. Eight years previously he had been treated for peptic ulcer which responded well to medication. The stools were never black or gray. He seldom vomited or complained of nausea.

Physical examination was essentially negative except for marked enlargement of the spleen which extended four fingers below the costal margin and was smooth and hard. The liver extended three fingers below the costal margin. The red blood cell count was 3,800,000 with 70 per cent hemoglobin. The white cell count was 5,150. Urinalysis, Wassermann reaction, blood urea (22 mg), creatinine (1.18 mg) and sugar (84 mg) were negative. An exploratory operation was performed and the spleen was found to be five times its normal size. There was thrombosis of the superior mesenteric vein and the veins along the greater and lesser curvatures of the stomach. There was some free fluid in the abdomen and the liver was fibrotic. No other masses were found. An operative diagnosis of Banti's disease was made. The patient developed an acute bronchopneumonia postoperatively. Clear ascitic fluid was forced through the wound by the excessive coughing. Following a stormy course the patient improved and was discharged five weeks later. He was readmitted two months later with epigastric pain, nausea and vomiting lasting three days following an intense family quarrel. Physical examination was unchanged. No abdominal fluid was present. An incisional hernia was present. Bowel movements were normal, but he complained of vomiting after meals. Active intestinal peristalsis was visible. There were large superficial veins over the chest and abdomen. A diagnosis of portal obstruction due to advanced Banti's syndrome was made. Laboratory findings revealed a red cell count of 3,600,000 with 70 per cent hemoglobin. The white cell count was 9,200 with 78 per cent polymorphonuclears. Urinalysis, blood chemistry and Wassermann reaction were again negative. Roentgen-rays were non-contributory. A diagnosis of intestinal obstruction was made and operation performed. In view of his poor condition splenectomy was impossible, but a loop of bowel caught in the adhesions was freed and enterostomy performed. Two transfusions of 500 c c blood each were given. Three days following operation he developed a sharp pain in the right axilla on breathing or coughing, which was thought to be due to a pulmonary infarction. However, this was not corroborated by roentgen-ray. A diagnosis of effusion was made, and 600 c c of clear fluid were removed the following day. The next day the patient became very weak and cyanotic and died. Autopsy was refused.

This case presents portal hypertension (splenomegaly, hepatic cirrhosis, ascites, enlarged superficial and deep veins) secondary to an advanced Banti's syndrome. The patient recovered from the thrombosis of the superior mesenteric vein and gastric veins probably by recanalization. The second attack of abdominal distress was precipitated by an intense family quarrel and emphasizes the influence of emotional excitement^{14, 15}.

The following case showed involvement of the small radicles of the portal system (esophageal, gastric, and splenic branches).

Case 7 E H, a white female, aged 62, complained of back pain, dyspnea and edema for one year, and anorexia for two months. There was a weight loss of nine pounds in two months. Past history was non-contributory except for a panhysterectomy and appendectomy 30 years previously.

Examination revealed essentially negative findings except for a markedly distended abdomen with dilatation of the veins on the abdominal wall and marked edema of the legs. No abdominal organs were palpable. Because of intolerance to mercurin, paracentesis was performed and yielded four gallons of clear yellow fluid. An-

other tap done two weeks later removed two gallons. Despite clays and supportive measures, the patient's abdominal pain was unrelieved and she got rapidly worse, dying six weeks after admission. Blood urea was 26 mg, creatinine 1.2 mg, sugar 88 mg per 100 cc. The abdominal fluid contained 374.4 mg protein per 100 cc and was negative for malignant cells. The clinical diagnosis was malignancy of the gastrointestinal tract with metastases.

Autopsy revealed five liters of thin clear reddish abdominal fluid. The liver weighed 1300 grams and showed typical portal cirrhosis. The gall-bladder contained half a dozen small faceted black mixed stones averaging 0.25 cm in diameter. The spleen weighed 125 grams and was essentially negative. The veins in the lower half of the esophagus were quite prominent and microscopically exhibited thrombosis with superficial mucosal ulcerations (figure 2). The portal and splenic veins and that por-

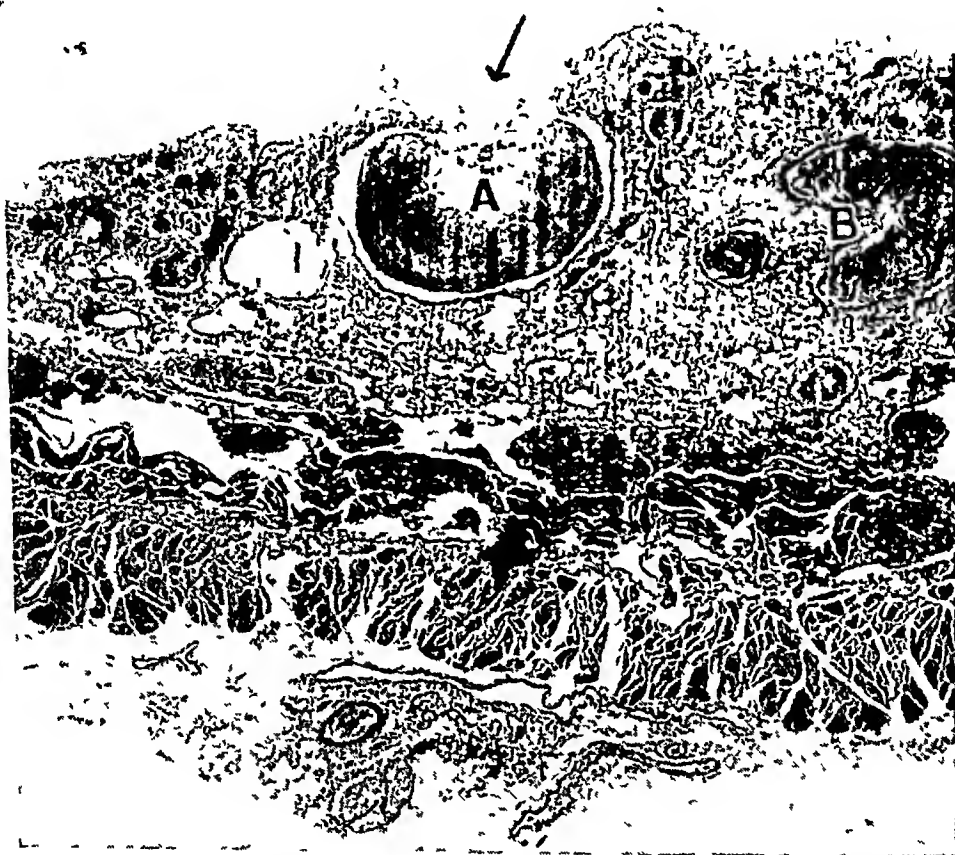


FIG 2 Thrombosis of varicose veins of the esophagus at A with superficial ulceration of mucosa and arrow demonstrating point of rupture of vein with resultant hemorrhage in Case 7. Another thrombosed vessel appears at B ($\times 17$)

tion of the inferior vena cava passing through the liver presented a markedly irregular and thickened intima of a phlebosclerotic nature. There was a chronic cholecystitis and chronic interstitial pancreatitis. The stomach contained a small amount of black fluid. The immediate cause of death was hypostatic pneumonia.

This case is of interest because it presents the unusual phenomenon of thrombus formation in the distant radicals of the portal system in a typical case of portal hypertension (figure 3).¹⁰ The resulting thromboses in the esophageal plexus gave rise to esophageal ulcerations. In addition, that por-

tion of the inferior vena cava passing through the liver, and the portal and splenic veins presented a markedly irregular and thickened intima. It is readily conceivable that these were fertile sites for the development of thrombosis. Had not the hypostatic pneumonia caused death in the interim. Another of our patients (Case 4) presented mesenteric and portal thromboses

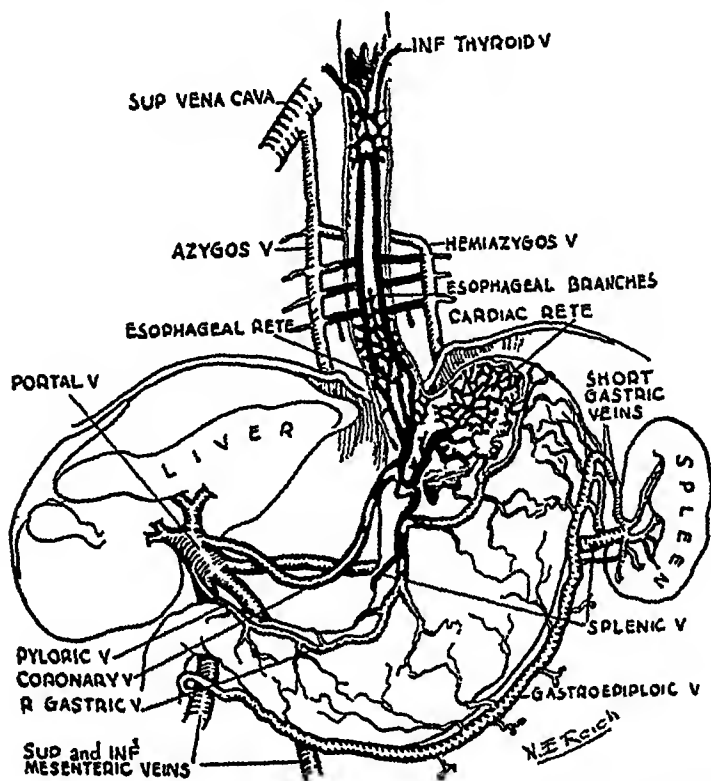


FIG 3 Portal circulation. Note that the upper third of the stomach and the esophagus have been exposed by removal of the anterior wall to show the formation of varices in the esophagus and cardia.¹⁹

with the presence of early thrombi in large tortuous esophageal varices. Still another showed marked thrombotic involvement of the gastric plexus (Case 6).

The following three cases presented thrombosis of the portal system associated with carcinoma.

Case 8 L. C., white tile-setter, aged 46, complained of sudden painless jaundice of three to four days' duration. A very bad cold preceded the onset. His stools had become light and the urine dark. No history of alcoholism or other illness could be obtained.

Physical examination revealed a moderately jaundiced male without other positive findings. A clinical diagnosis of catarrhal jaundice was made but the patient became rapidly worse and died after 10 days.

Laboratory examination showed the presence of both urinary bile and urobilinogen. Mucus and blood were found in the stool, but no bile. The icteric index increased from 50 units to 80 units. Total serum protein was 6.3 mg per 100 c c blood, albumin 3.3, globulin 3.0, with a ratio of 1.1.

TABLE I

Case	Name	Age	Sex	Duration of Present Illness	Ascites *		Spleen †		Liver		Pathology of Vascular System	Associated Pathology
					Clear	Blood	Weight	f b c m	Weight	f b c m		
1.	E M	72	M	15 days	4 plus	0	230 gm	0	920 gm	0	Circumscribed soft necrotic dark brown nodule in portal vein occluding lumen and extending into liver	Portal cirrhosis, lobar pneumonia, cholelithiasis
2	A M	63	M	3 weeks	4 plus	0	480	0	2700	3	Nodular yellow mass in portal vein plus few small projections pressing from without	Non-specific granuloma of gall-bladder, obstructive biliary cirrhosis and portal cirrhosis.
3	J L	65	M	1 day	0	0	small, no weight given	0	1000	0	Complete occlusion of superior mesenteric vein with fresh thrombus	Portal cirrhosis with chronic hepatitis and focal necrosis, obstructing common duct stone, intestinal gangrene, biliary fistula
4.	J M	55	M	1 week	4 plus	plus	240	0	1400	‡	Adherent thrombus with intimal thickening and edema Vacuolization of media Involvement of both portal vein and superior mesenteric vein	Marked portal cirrhosis, cholelithiasis, arteriosclerotic heart disease, acute and chronic cholecystitis, acute suppurative peritonitis following paracentesis
5	J D.	45	M	5 days	4 plus	0	450	0	1310	0	Fresh thrombosis of superior mesenteric vein	Marked portal cirrhosis, bronchopneumonia; pulmonary infarctions

TABLE I—Continued

Case	Name	Age	Sex	Duration of Present Illness	Ascites *		Spleen †		Liver		Pathology of Vascular System	Associated Pathology
					Clear	Blood	Weight	f b c m	Weight	f b c m		
6	M W	41	M	3 days	2 plus	0	5 X norm size at operation	4	no autopsy	3	Thrombosis of superior mesenteric and gastric veins with recanalization	Banti's syndrome, pulmonary artery embolism
7	E H	62	F	1 year	4 plus	0	125	0	1300	0	Portal and splenic veins markedly thickened with irregular lumen Thrombosis of the esophageal veins	Portal cirrhosis, hypostatic bronchopneumonia
8	L C	46	M	4 days	3 plus	1 plus	450	0	2400	0	Thickened intima of fibroblasts and capillaries merges with the organizing occluding thrombus In the folds of the thrombus are small groups of adenocarcinomatous cells	Portal cirrhosis, adenocarcinoma of liver with lung metastases, bronchopneumonia
9	A M	65	M	1 month	4 plus	1 plus	130	0	2000	?	Thrombus at entrance of portal vein into liver, also in splenic and pancreatic veins Splenic and pulmonary artery thrombosis	Portal cirrhosis, adenocarcinoma tail pancreas with metastases, bronchopneumonia
10	A H	57	M	8 weeks	4 plus	0	540	0	2600	2	Complete thrombosis of portal, mesenteric and splenic veins, large varices of fundus of stomach with thrombi	Portal cirrhosis, primary carcinoma of the liver

* Ascites—1 plus—100 c c, 2 plus—100–500 c c, 3 plus—500–1000 c c, 4 plus—over 1000 c c
† f b c m —fingers-breadth below costal margin

TABLE II
Symptoms and Findings

Case	Name	Abdominal Pain	Intestinal Obstruction	Diarrhea	Constipation	Toxemia	Jaundice	Gastroint Bleeding
1	E M	4 plus R U Q	0	0	0	2 plus	1 plus	0
2	A M	0	0	0	1 plus	2 plus	3 plus	4 plus esoph, gast, and intest.
3	J L	4 plus R U Q	1 plus	0	0	2 plus	4 plus obstructive	0
4	J M	2 plus	0	0	0	0	1 plus	0
5	J D	4 plus lower abd	4 plus	0	1 plus	4 plus	0	4 plus rectal
6	M W	3 plus epigastric	4 plus	0	0	1 plus	0	0
7	M H	4 plus abd and back	0	0	0	0	0	4 plus esoph
8	L C	1 plus right flank	0	1 plus	0	2 plus	4 plus	1 plus
9	A M	0	0	1 plus	0	0	0	0
10	A H	4 plus stomach	0	0	1 plus	0	1 plus	0

At autopsy, the portal vein was moderately distended and when opened, a thick soft friable mass of yellow tissue escaped under pressure and filled the lumen from the porta to the level of the cystic duct. Below this level, the lumen was partially filled with a moderately friable dark grayish-red blood clot which clung tenaciously to the wall and extended a short distance into the splenic veins. The thin fibrous adventitia and the media showed many large congested blood vessels with mild perivascular infiltration. The thickened intima, composed of fibroblasts and capillaries, merged with the peripheral organizing zone of the large thrombus that occluded the lumen. The thrombus consisted of irregularly anastomosing cords of necrotic platelets and leukocytic material. Among these were found red cells suspended in fibrin. In the folds of the fibrin were tiny nests of adenocarcinomatous cell metastases. The peritoneal cavity contained a red watery fluid in the lesser and greater omental cavities. Neither fibrin nor clot was encountered in the thin fluid. The liver weighed 2400 gm and was typical of atrophic cirrhosis but also presented primary adenocarcinoma of the right lobe with extensive pulmonary metastases. The spleen was enlarged, weighing 450 gm.

In addition to the typical atrophic cirrhosis, the primary adenocarcinoma of the liver also played an important rôle in the production of the portal system thrombosis. It is possible that the yellow tissue extending from the porta of the liver to the cystic duct was of a carcinomatous nature. Subsequently, the remainder of the lumen became filled with dark grayish-red blood clot which then extended a short distance into the splenic veins. Ac-

cording to Rolleston and McNee,²⁰ intra-abdominal malignancy in general is second to cirrhosis of the liver in the production of portal thrombosis. In the case of a hepatic carcinoma, the portal vein ordinarily becomes invaded by direct extension of malignant tissue, although pressure and injury to the vein wall may play additional rôles. Langdon-Brown¹ states that of 41 collected cases of portal vein thrombosis, malignant disease alone was present in seven cases (15 per cent), yet in only two of these did the obstruction which led to the thrombosis appear to be intrahepatic. He is of the opinion that malignant disease of the liver favors the occurrence of thrombosis by the portal stagnation it produces.

Case 9 A M, white male, aged 65, complained of weight loss of 50 pounds in nine months. Occasional vomiting occurred immediately following ingestion of meat, but after no other foods. There was marked anorexia. Sometimes for a few days he had two to three watery stools daily. There was no history of previous illnesses.

Physical examination revealed a patient with evidence of recent weight loss but in no acute distress. There were no masses or any positive physical findings. A diagnosis of possible gastric neoplasm was considered. Laboratory tests, including gastric analysis, were negative, except that the blood sugar was 177 mg and the urine showed one plus sugar on two occasions with no ketone bodies and the blood urea was 75 mg per 100 c c. The patient died two days after admission.

Postmortem examination revealed an adenocarcinoma of the tail of the pancreas, weighing 1250 grams, with metastases to liver, gall-bladder, left adrenal, spleen, portal and periaortic glands, diaphragm, lungs, omentum, and mesentery (figure 4). There was also extensive portal cirrhosis. The portal vein was occluded at its entry into the liver by a fresh thrombus. In addition, the splenic and pancreatic veins were similarly involved, as were the pulmonary and splenic arteries. There were 1000 c c of hemorrhagic ascitic fluid. The adenocarcinoma of the tail of the pancreas undoubtedly played a rôle.

According to Webster⁴ and others,^{7, 21, 22} obstruction of the portal vein flow occurs as a result of the mechanical pressure of pancreatic carcinoma. Occasionally, injury to the vessel wall and direct extension are also noted. This case is also interesting because of the involvement of the tail without jaundice, whereas all other references are made to carcinomatous involvement of the head or body. Langdon-Brown¹ reports three cases of carcinoma of the head of the pancreas which pressed upon, narrowed and wrinkled the portal vein in its course.

Case 10 A H, a white male, aged 57, was admitted complaining of pain in the stomach of eight weeks' duration. It was constant, knifelike, and prevented sleep. His appetite was poor and he was constipated, with occasional nausea but no vomiting or tarry stools. His past history revealed that he had been taking digitalis because of swollen ankles. The right foot had been amputated one year earlier because of severe trauma with resulting gangrene.

Physical examination revealed a thin emaciated male with normal temperature, pulse and respirations. There was slight icterus of the skin. The heart showed a slight apical systolic murmur but no enlargement. The liver was felt two fingers below the costal margin and was hard and nodular. There was moderate ascites and pitting edema of the legs. Paracentesis yielded 3000 c c of clear yellow fluid with a specific gravity of 1.010, and 4 plus albumin. Urine was negative. The patient died two days after admission.

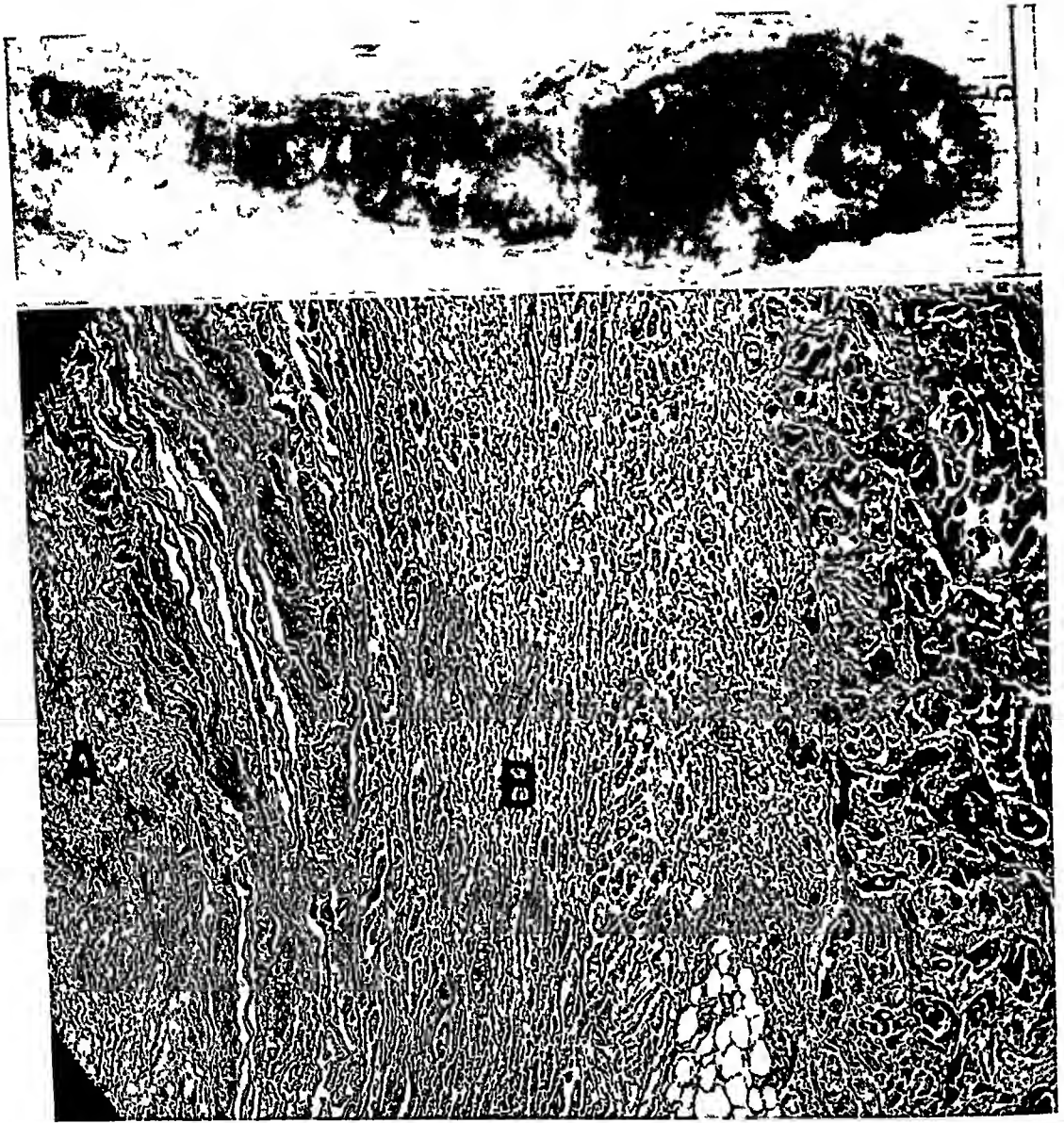


FIG 4 (*Above*) Adenocarcinoma of the tail of the pancreas weighing 1250 grams with extensive metastases in Case 9. The malignancy was soft and beefy red whereas the pancreas was firm and gray. In addition, there was portal vein thrombosis, pulmonary artery thrombosis and splenic infarction. (*Below*) Section illustrating A thrombus, B thickened portal vein wall, and C metastatic invasion of vein ($\times 60$)

Autopsy revealed portal cirrhosis of the liver, primary carcinoma of the bile duct-cell type, with metastases to the lungs, diaphragm, and regional lymph nodes, complete thrombosis of the portal, mesenteric and splenic veins, large varices of the stomach fundus with thrombi, marked congestion of the spleen, and leiomyoma of the esophagus. There were two liters of clear ascitic fluid. The liver weighed 2600 gm, the spleen 540 gm. The heart weighed 320 gm and was entirely negative. There was a thrombotic occlusion one centimeter long in the left common carotid artery.

The evidence of portal hypertension in this case is conclusive (marked splenomegaly, clear ascites, gastric varices, portal cirrhosis). How much pressure the carcinoma caused is, of course, difficult to ascertain. The thrombi and vessels failed to show metastatic foci. It is worthy of note that

gastrointestinal symptoms predominate when the mesenteric or gastric veins are thrombosed (also case 6)

ETIOLOGY

Many factors of varying importance are at work in the production of aseptic thrombosis of the portal system in portal hypertension

A Blood Flow Changes Perhaps the most important of these factors accounting for the high incidence of thrombosis in portal hypertension are blood flow changes occurring as a result of the intrahepatic venous obstruction. Ordinarily, pressure in the portal vein is 5 mm of mercury, and that in the hepatic vein is from 0 to —0.8 mm mercury²³. This difference in pressures is one of the factors which allows the intrahepatic flow to be completed in eight seconds. Thompson and his co-workers²⁴ were able to measure the tension within the splenic vein at the time of splenectomy in Banti's syndrome and found it to range from 250 to 500 mm of saline. Five cases were due to atrophic cirrhosis whereas the remaining three were due to cirrhosis caused by chronic schistosomiasis. The antecubital pressure taken simultaneously ranged from 120 to 140 mm. In one of our own cases (J A) of Banti's disease (not reported here because of the absence of thrombosis) a venous pressure manometer attached to the splenic vein at the time of splenectomy showed a pressure of 260 mm of water compared to an arm venous pressure of only 150 mm. Claude Bernard showed originally that the ligation of the portal vein does not deprive the liver of its blood supply, since a backflow from the hepatic veins occurs. Thus, obstruction of short duration will not cause continued splenic enlargement. Warthin was unable to cause permanent splenomegaly by tying the splenic vein. In addition, the distensibility of the spleen and intestines, as well as the portorenal anastomoses, helps to maintain normal portal tension. When the blood passage becomes obstructed through the liver, the resulting anastomoses (figure 3) bring about a number of unexpected changes identifiable under the syndrome of portal hypertension²⁵. These give rise to dilatation of two large anastomoses, the deep visceral and superficial parietal plexi^{19, 23}. Histologically, the most important changes present are the intrahepatic venous lesions to be described shortly. These result in intrahepatic strangulation of the branches with slowed blood flow. The spleen undergoes a congestive hypertrophy with secondary inflammation and sclerosis⁶. The pancreatic changes are variable, being either atrophic or hypertrophic. The gastrointestinal tract presents hemorrhages and disturbances in food and water absorption. Vascularized peritoneal adhesions and portorenal anastomotic changes complete the picture. It is well to remember that in cirrhosis the collateral circulation tends to be established in a direction away from the damaged liver into the peripheral circulation. In portal vein thrombosis the collateral circulation is around the occluded portion of the vein toward the still functioning liver.

B Changes in the Veins The result of portal hypertension is a passive dilatation of the entire system, slowed circulation and increased pressure in the portal radicles which eventually cause a compensatory hypertrophy of the muscular coat of the vein,²⁷ with endophlebitis and periphlebitis frequently adding to the circulatory difficulties. This process may occur down to the smallest portal vein branches in advanced cases. L¹²⁹ summarized the changes in the portal system in portal hypertension as follows: (1) muscular hypertrophy of the media, and (2) intimal thickening with development of the longitudinal muscle beneath it. Actually, calcareous plaques may project into the lumen with subsequent thrombosis (Case 2). Primary portal phlebosclerosis as recently reported by us,²⁸ must be differentiated. It produces portal hypertension by virtue of its sclerosis and narrowing of the portal system but occurs in young persons with leukopenia and without ascites or anemia. Phlebosclerosis occurred in 35 per cent of Borrmann's cases¹⁰ of portal vein thrombosis. Webster⁴ believes that it is always accompanied by sclerotic changes in the walls of the portal vein and its branches. Indeed, the walls may become completely ossified, forming a sheath³⁰. The roots of the portal vein, especially in the lower third of the esophagus, will show large varicosities and microscopic changes very well^{10, 31}. Aside from the possibility of hemorrhage, thrombus formation on the wall of such damaged veins is quite possible, especially in view of the slowed blood flow and other factors to be mentioned. A discussion of the venous changes would be incomplete without mentioning the possibility of a secondary adhesive pyelphlebitis²⁰ due to an extension from cholelithiasis with cholangitis, hepatitis, cholecystitis, infarction and inflammation of the spleen, and pancreatitis—all of which veins drain into the portal system and frequently complicate ordinary cirrhosis of the liver. In addition, they may be caused by subphrenic abscess and suppurating mesenteric lymphadenitis. However, recent experiments by Tannenbergl³² tend to prove the relative unimportance of normal venous endothelium and its reactivity in the pathogenesis of thrombosis. This is a reversal of the formerly accepted views of Klemensiewicz⁹ and his collaborators that a jelly-like membrane of homogeneous fibrin at the wall of a blood vessel is the primary and decisive factor in the development of a thrombus. Rousselot³³ emphasized the dilatation and tortuosity of the veins in the splenic pedicle and found them from two to four times the normal diameter in congestive splenomegaly. In half there was evidence of obstruction at the time of operation.

C Gastrointestinal Changes Favoring Thrombosis The catarrhal gastroenteritis which liver cirrhosis produces favors bacterial invasion of the portal vein branches. The occurrence was 3.3 per cent in the L. Brown³⁴ series, whereas it was 9 per cent in the Lissauer⁷ statistics. Webster⁴ found the percentage in liver cirrhosis to be 2.6. It has been demonstrated by Green¹⁵ that an unhealthy state of the gastrointestinal tract (e.g., appendectomies or gastrointestinal allergies) was actually able to produce mesenteric thrombosis in young people whose vessels were free from arterio-

sclerosis or other disease According to this author, it is also probable that the mucosa of the intestinal tract, under pathologic conditions such as occur in liver cirrhosis, is impaired in the production of antithrombin, which according to all available knowledge is derived from tissues of endodermal origin (liver, menstruating uterus, salivary glands, and peptone from the stomach glands acting on protein) This may conceivably exert an additional influence on the formation of thrombosis

D Syphilitic Vascular Changes and Tuberculosis Syphilis has been established by Sinimonds,¹¹ although originally mentioned by others,^{35, 36} as an etiological factor by causing degeneration and exudation in the media and other coats of the veins with fibrosis of the liver Thrombosis is found in both the hereditary and acquired forms of the disease In 10 per cent of Lissauer's cases⁷ a syphilitic pylephlebitis produced liver syphilis with thrombosis Syphilis was originally claimed by Warthin³⁷ to be the most common cause for thrombosis Tuberculosis, whether peritoneal or hepatic, is also found in association with portal hypertension and may produce cirrhosis In fact, about 20 per cent of cirrhotic cases develop tuberculosis terminally Cancer of the liver may also manifest symptoms of portal hypertension

E Postoperative Thrombocythemia Splenomegaly is frequently so marked in cirrhosis of the liver as to warrant splenectomy When splenectomy is not done, intestinal infarction is common The removed spleens in the Weir and Beaver² series weighed from 800 to 1600 gm When splenectomy was performed, thrombosis was found in the portal and splenic veins as a terminal event and had little to do with the course of the primary disease It has been described in the mesenteric vein following splenectomy as long ago as 1895³⁸ It is directly attributable to the marked rise in platelets following splenectomy Extensive thrombosis is likely to occur in cases with normal or very slightly subnormal platelet count before operation³⁹ Following splenectomy the count may be elevated and remain at 1,000,000 per cu mm^{40, 41} The fibrin may be increased following operation, the average being 41 per cent In most cases, however, a fresh thrombosis formed during the postoperative period is found superimposed on a chronic process Essential thrombophilia may produce sudden occlusion similarly

F Pressure of Ascitic Fluid The massive abdominal effusion of portal hypertension may aid in pressing on and obstructing blood flow in the portal system

G Traction of adhesions about the portal system or from chronic peritonitis may also cause slow occlusion Numerous cases are reported^{1, 33} in which trauma from blows to the abdomen has produced thrombosis of the portal system Trauma may also be produced by volvulus and kinking of the mesentery

H Increased viscosity of blood occurs due to the dehydrating measures employed in liver cirrhosis, loss of fluids in edema and ascites, hemorrhage, and the increased platelets and fibrinogen following any operation In addi-

tion, there is an initial drop in pressure which aids in clot formation. Response to physiological emergencies may cause variations of 10 per cent or more in the specific gravity of blood. Thus, in excitement, a long recognized factor,¹² the spleen contracts and a large number of red cells is poured into the blood¹³ (Case 6). This can be repeated experimentally by injections of adrenalin which, by partially diminishing the size of the spleen, reduces the clotting time of blood to half. The trauma of splenectomy or other operation may also result in loss of fluids and a diminished blood volume. In addition, vomiting, diarrhea, diuresis and acidosis all tend to elevate the serum protein concentration. The fact that thrombosis may occur in different blood systems of the body (e.g., pulmonary artery and portal vein of Case 9) speaks strongly for an influence of this factor. Hypochloremia may be associated in some way with intravascular clotting. Death may be produced from thrombosis due to polycythemia rubra vera.¹⁴ A more detailed consideration of the influence of various blood factors is to appear shortly.^{15a}

I Introduction of intravenous tissue extracts has been shown experimentally and clinically to cause portal thrombosis. As far back as 1901 it was shown that the injection of nucleoproteids induced portal vein thrombosis, and if the animals survived the liver infarctions, early cirrhotic changes occurred.¹ Liver extracts and other opotherapies employed in the treatment of cirrhosis might possibly produce this condition.¹⁵ It is known that rapid injection of a tissue extract (particularly lung, thymus or lymph glands) supplies thrombokinase and results in the gradual deposition of fibrin upon the vascular walls.^{4, 16a} However, many aspects of this phenomenon await elucidation.

J Chemical and toxic factors, although unproved, may be added to the other causes since it is well to remember that only portal blood contains the undetoxified products of the digestive tract. Pallette³ and Warren and Eberhard¹³ report six cases of venous mesenteric thrombosis following acute alcoholic intoxication. Arsenicals and other hepatic poisons also find their way to the liver through the vulnerable portal system. According to Best and Taylor,^{43a} injuries by chemical, mechanical or infective agencies cause the liberation of thrombokinase from the injured vascular wall.

K Other Diseases Producing Portal Hypertension Besides the cases of portal cirrhosis and splenic or portal thrombosis, we must consider also the unclassified hepatic cirrhosis,¹⁹ schistosomiasis,^{17, 33, 46} splenic anemia and Banti's syndrome, and primary disease of the portal vein^{21, 22, 30, 47} (primary portal phlebosclerosis²⁸).

(a) *Schistosoma mansoni* (Africa, West Indies) is the species of blood-fluke (trematode) responsible for intestinal bilharziasis. The ova accumulate in the walls of the large bowel and liver giving rise to hepatic cirrhosis at times from the formation of pseudotubercles about the ova deposited in the liver. Splenomegaly is probably secondary to the cirrhosis. *Schistosoma japonicum* (China, Japan, Philippines) inhabits the veins or arteries of the

intestines and other organs giving rise to liver cirrhosis, progressive anemia, splenomegaly, ascites, and dysentery *Bilharzia hematobia* (blood fluke) infects about one-fourth the Egyptian population and the parasite may be found in the portal vein, the splenic and mesenteric veins, and the blood vessels of the bladder and rectum

(b) In splenic anemia and Banti's syndrome, although the etiology still remains essentially obscure, there is a progressive sclerosis of the splenic and portal veins^{28, 48} In 66 per cent of the cases in the Evans⁴¹ series of Banti's syndrome, portal and splenic vein thrombosis occurred secondary to cirrhotic liver changes This may give rise to splenomegaly In the remaining 34 per cent, thrombosis occurring in the absence of cirrhosis appeared to be the cause of Banti's syndrome A toxic factor, which may be causative, either originates in the spleen or first affects it, and is then poured into the liver to produce the cirrhotic and fatty changes as well as the focal and central necrosis Even the walls of the splenic venules are thickened, but they do not become dilated as in passive congestion of the spleen

(c) Finally, hemangioma as a primary disease must be considered The duration of this condition varies from two months to 27 years^{49, 50} The spongy, vascular tissue changes may be found in the hepatoduodenal ligament as well as the vasa vasorum of the portal vein In reviewing the literature on cavernomatous transformation of the portal vein, Klemperer⁵¹ adds a case to nine others collected from the literature in which this condition produced symptoms of portal hypertension They could be classified into three groups representing (1) the end result of portal thrombosis, (2) malformations, and (3) tumor (angioma) of the vein However, there is considerable difference of opinion as to whether the cavernous or angiomatous type is the result of thrombosis or is a true neoplasm

SYMPTOMS

It is well not to confuse the chronic symptomatology of the underlying disease with that of the superimposed thrombosis In cirrhosis with ascites, gastrointestinal symptoms, and splenomegaly, portal thrombosis may be easily overlooked The duration of illness in our series ranged from one day to seven years The acute forms are not very important clinically since they usually occur as terminal events They may produce either no symptoms at all or none that is definite and, therefore, almost always fail to be diagnosed When the obstruction is gradual (which is more usual) with the formation of a collateral circulation, the symptomatology may resemble that of chronic splenic anemia When the block is sudden, ascites and hematemesis or intestinal hemorrhage appear shortly, followed by death However, hematemesis may occur over long periods of time Brahme⁵² reports a case of splenic vein thrombosis that had repeated attacks of hematemesis for 45 years Ascites was found in 65 per cent of Rolleston's series,⁶ whereas it was present in 90 per cent of our cases and was bloody in

two cases. Chronic occlusion of the portal vein may run a long course over a period of many years. The most frequent signs are ascites, abdominal pain, hematemesis and splenomegaly. Jaundice may exist less frequently (31.6 per cent) according to others and was present in five of our cases (50 per cent). Gastric hemorrhages which occurred months or years previously and which were even mild or transitory are one of the most important symptoms in the history. The spleen was palpable in only one of our cases (Banti's disease), whereas the liver was palpable on four occasions.

When the acute thrombosis is confined to the splenic vein, the picture becomes one of sudden splenic tumor. Wohlwill¹⁸ emphasized the fact that definite splenic thrombosis is not always accompanied by splenomegaly. There may be colicky pains in the left hypochondrium and signs of perisplenitis and local peritonitis. Gastric symptoms are common in the chronic form although the splenomegaly may be present for years without symptoms. Johnston⁵³ showed that when an obstructive factor is present the splenomegaly will be greater in younger patients. Toxemia was a prominent finding in five of our own cases.

Thrombosis in the mesenteric veins results in infarction of the intestines with colicky pains, peritoneal irritation, and bloody diarrhea. Although the blood picture is not characteristic, a leukopenia may be present. Opitz⁵⁴ described a striking decrease in the size of the spleen after a severe gastric hemorrhage. It resembles the experimental effect induced by adrenalin injections. This is least pronounced in those cases due to Banti's syndrome. Eppinger⁵⁵ observed glycosuria twice due to a concomitant pancreatitis which so frequently complicates a cirrhotic liver. The failure of the portal blood to reach the hepatic vein because of an obstruction results in a venous hypotension in that vein resulting in arterial hypotension with a small heart, tachycardia, and oliguria.

Associated Venous Thrombosis According to Weir and Beaver,² about one-third of the cases of thrombosis are associated with thrombosis of distant arteries and veins. Rolleston and McNee²⁰ are of the opinion that thrombosis of the portal vein may occur secondarily to thrombosis of the hepatic veins. However, in portal cirrhosis thrombosis of the hepatic vein is rare. It may be due to intercurrent infections superimposed on the cirrhosis, involving the walls of these veins. But in some cases of thrombosis, in which there is a slight amount of cirrhosis, it may be due to secondary fibrous replacement.

Evans⁵⁶ and Byrom⁵⁷ believe that Chiari's disease is closely allied to the thrombotic type of Banti's disease and cirrhosis, the symptoms depending on whether the clotting occurs in the hepatic or splenic veins. In fact, Evans⁵⁶ cites a case in which portal vein thrombosis is caused by Chiari's disease. The clinical and postmortem studies of a case of Budd's⁵⁸ (or Chiari's) disease are reported in which thromboses of the hepatic veins and of the inferior vena cava were found in association with eye conditions. Venous thrombosis in the mesenteric radicals shows a tendency to extend so that ad-

ditional segments may become involved ⁵⁹ (Case 4) Cabot ⁶⁰ reports a case in which a thrombosis of the superior mesenteric vein extended to the portal, splenic and pancreatic veins, in addition to which there was found a partial obstruction of the inferior vena cava by an old sclerosed thrombus with collateral circulation through the left ovarian vein Two of our cases (5 and 9) showed evidences of associated venous thrombosis, the latter of an extensive nature

PROGNOSIS

The prognosis depends mainly upon the primary cause This is also dependent upon the stage of development of the primary disorder and the extent of the thrombosis as well as its acuteness If there is a gradual development, life may carry on for two years or longer In general, however, the acuteness of the condition and completeness of occlusion result in death shortly after the appearance of the thrombosis This is due to circulatory failure because of the extensive loss of blood from the general circulation into the trapped splanchnic area Similar results have been obtained experimentally ⁶¹ Donaldson and Stout ⁶² describe thrombosis of the mesenteric arteries and of the veins as separate entities Thrombosis of the veins is less serious and spontaneous recovery occurs in about half the cases This is because the arterial supply continues, collateral venous channels are utilized, and the lymphatics remove part of the venous load If early diagnosis is made in mesenteric vein thrombosis, recovery is possible Green ¹⁵ reports four recovered cases of mesenteric vein thrombosis, following early operative interference

TREATMENT

The preventive treatment of portal thrombosis should be directed to an early arrest of the underlying disease in an effort to relieve the portal hypertension and improve the collateral circulation In atrophic cirrhosis this would consist of the administration of diuretics (ammonium chloride and mercupurin) with salt and fluid restriction for the ascites and edema, a high carbohydrate diet (400 grams) because it effects a definite reduction in fibrinogen, ⁴⁵ with insulin (5 units increasing to 15 units three times daily) for increased liver nutrition, liver extract, high vitamin intake (especially vitamin B complex), and bland foods if esophageal varices exist Greene ⁶³ recommends the use of high protein diets to combat the hypoproteinemia and the transfusion of ascitic fluids when the protein content is high in selected cases The etiological cause of the cirrhosis must be removed (alcohol, arsenic, and poisons), or treated (syphilis, malaria, hyperthyroidism, tuberculosis, and cholelithiasis) Splenic anemia and Banti's syndrome necessitate the removal of the spleen

Chronic thrombosis of the portal system is usually uninfluenced by treatment Ligation of the great collateral veins should be avoided in splenic thrombosis because frequently fatal gastric hemorrhage follows

Talma's operation or some modification thereof should be attempted instead Splenectomy is contraindicated regardless of the size of the spleen because of postoperative thrombocythemia, slowing of circulation, and embolization Occasionally tapping may be necessary to relieve the ascites Resection of the gangrenous gut is, of course, imperative in mesenteric thrombosis Green¹⁵ and Curiy and Backus¹⁶ report cases successfully operated upon Transfusion is vital in massive hemorrhage Among the newer drugs, Lurz and Klingen¹⁴ have advocated the use of metiazol and quinine but obtained variable results Adovern, a glucoside of *adonis vernalis*, has been employed by Mylenbusch¹⁵ From abundant experimental and clinical use, it has been shown that heparin will prevent thrombosis in the systemic circulation Gordon and MacKenzie¹⁶ showed clinically and experimentally with dogs that it can be of great use in preventing thrombosis of the portal vein following splenectomy and especially following resection of the bowel for mesenteric thrombosis Heparin is given intravenously in sufficient quantity to raise the clotting time to about 15 minutes Frequent intravenous injections¹⁷ of sodium citrate have been employed

CONCLUSIONS

- 1 The importance of portal system thrombosis occurring with the portal hypertension syndrome is stressed
- 2 The responsibility of different factors, acting singly or in combination in the production of portal thrombosis, is considered
- 3 The incidence, symptomatology, associated venous thrombosis, prognosis, and treatment are reviewed
- 4 Ten autopsied or operated cases of portal system thrombosis associated with portal hypertension are described, nine due to atrophic cirrhosis and one due to Banti's syndrome

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A DIAGNOSTIC SIGN OF SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE MEDIAS-TINUM; CASE REPORTS *

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IN our experience with the male student body at the University of Kentucky, the incidence of spontaneous (idiopathic) pneumothorax is about one case per year per 1000 male students¹ In one of the cases previously reported, a "popping" or "crunching" sound was heard over the precordium which was audible to the patient Of four cases of spontaneous pneumothorax observed by the author since this paper was written, three presented this phenomenon Hamman² has observed this sign and feels that it is pathognomonic of mediastinal emphysema, a step in the occurrence of spontaneous pneumothorax So few simple physical signs are absolutely diagnostic that any one such should receive sufficient study to establish or discredit its value With this thought in mind the following case reports are presented

CASE REPORTS

Case 1 L M, aged 18, male, white, college student, was first seen October 25, 1940 The evening before, while sitting in his room studying, he experienced a sharp pain in the region of his heart The pain was not severe but continued without relief There was some difficulty in breathing Physical examination showed some suppression of breath sounds on the left side Roentgen-ray confirmed the diagnosis of spontaneous pneumothorax on the left side, with the lung separated from the chest wall by about 3 cm There was a small amount of fluid at the base On October 28, 1940, the patient was still quite uncomfortable, with pain and a sense of something shifting in his chest when changing his position He became conscious of a "crunching" sound in his chest This was audible through the stethoscope of the examiner On October 29, 1940, pain developed in the lower thoracic region posteriorly, and later shifted to his upper abdomen There was an area of tympany in his left upper abdomen, pressure over which gave him considerable pain This was interpreted as probably being a collection of retroperitoneal air This pain subsided October 31, 1940 The snapping sound over the precordium was still faintly audible November 4, 1940, although a roentgen-ray at this time showed that considerable expansion had taken place The fluid had been absorbed Recovery was prompt and uneventful

Case 2 P H, aged 20, male, white, college student, was seen by the writer with Dr J S Chambers, with diagnosis of spontaneous pneumothorax On November 14, 1940, the patient was working in the University printing office He was engaged in handling type sets which weighed about two pounds each The pain in the left side of his chest came on suddenly and persisted He was aware of a faint "popping" or "crackling" sound in his chest This was readily heard with the stethoscope Roentgen-ray confirmed the diagnosis of spontaneous pneumothorax with partial collapse of the left lung There was a very small amount of fluid present On November 22, 1940, he still had slight pain Hamman's sign was still present

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Roentgen-ray showed partial absorption of the air. There was no sign of fluid. Recovery was uneventful. The patient related that he had had similar attacks in 1936 and 1937, but no roentgenogram was made.

Case 3 H. B., aged 18, male, white, candidate for admission to the University of Kentucky. On February 5, 1941, while doing a routine physical examination on this prospective student, which is required of all entering freshmen, the writer heard rather faint but characteristic "crunching" sounds over the precordium. This was heard with the patient sitting or supine. He himself had not heard these sounds. Further examination revealed signs of a partial pneumothorax on the left side. He was told that he had a partially collapsed lung from pneumothorax, and the following history was obtained. On February 2, 1941, while playing trombone with a dance orchestra, he experienced a sudden sharp pain in the left side of his chest. It was difficult for him to continue playing, and the pain was worse when he went home. A physician was called who told him that he had intercostal neuralgia.

Roentgen-ray of his chest confirmed the diagnosis. Recovery was uneventful.

DISCUSSION

Two of the above patients had experienced a recent cold. They were all tall and moderately underweight. This observation may not be significant, but the tall, thin body type has been predominant in our cases.

The mechanism of Hamman's sign is probably the presence of bubbles of interstitial emphysema overlying the pericardium as suggested by Hamman. That concurrent interstitial emphysema is common with many cases of spontaneous pneumothorax, and indeed a step in the mechanism, is borne out experimentally by Macklin,³ by the author and associates,¹ and by others.^{3, 4}

As far as I am aware, all the reported cases showing Hamman's sign have had pneumothorax of the left side.⁵ If the sounds were produced simply by air in the pleural space, then it should have been observed frequently in the routine of therapeutic pneumothorax.

The sound, if not loud, might be mistaken for noise produced by the rubbing of the stethoscope bell over the skin, or the rubbing of the stethoscope tubing together. I feel that the description previously given of rubbing two inflated rubber balloons together, or pinching an inflated balloon and allowing the fingers to slip over the surface¹ is a good description of the sounds heard.

SUMMARY AND CONCLUSIONS

Three cases of spontaneous pneumothorax of the left side were observed, each of which presented the peculiar crackling sounds referred to as Hamman's sign.

One case gave signs and symptoms suggesting retroperitoneal air, which is a common finding in animals in which over inflation pneumothorax has been produced experimentally.

The peculiar crackling sounds heard in the chest, as described, are probably pathognomonic of mediastinal emphysema, which is a step in the mechanism of some cases of spontaneous pneumothorax.

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THE OCCURRENCE OF PERIPHERAL FACIAL PARALYSIS IN HYPERTENSIVE VASCULAR DISEASE¹

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ALTHOUGH paralysis of the peripheral portion of the facial nerve is a very common disorder, its occurrence as a result of localized compressive bleeding in hypertensive vascular disease has been regarded as rare. Whereas hemorrhage into the facial aqueduct as a cause of facial palsy was recognized by earlier observers, their pathological findings and opinions have been ignored recently in the tabulated causal classifications of facial paralysis.

Since 1925, 468 cases of facial paralysis peripheral in location have been observed. Eighteen of this number were myoclonic facial palsies. Although the ultimate picture of myoclonic paralysis resembles that of the contracted state of a peripheral facial palsy, the dubious nature of its cause hardly warrants its inclusion among the peripheral facial palsies. Of the 450 remaining cases 329 belonged to the group originally described by Bell, namely a paralysis of undetermined origin, but probably a Fallopiian neuritis. Twenty-four cases have been studied in which paralysis of the facial nerve was associated with hypertensive vascular disease, and 16 of this hypertensive group presented a certain constancy of onset which warrants setting them apart on the etiologic basis of paralysis resulting from hemorrhagic compression within the facial aqueduct.

REVIEW OF LITERATURE

Moxon¹ in 1869 reported the pathological examination of a patient suffering from a peripheral facial palsy in association with hypertension, and noted the following changes: "This specimen consists of part of the right temporal bone, with the horizontal part of the canal of the facial nerve exposed. At the point of junction of the Vidian nerve with the facial, an effusion of blood is found extending as far as the tympanum, it is dark and partly clotted, the Vidian nerve will be seen passing into it (that nerve is supported by a white bristle). The facial nerve, followed up to it, is found to be scarcely traceable further, being lost in the clot. It is probable that this effusion of blood is of the same nature as those common effusions of blood into the retina with which all are familiar. And in this light the case is interesting as a singular example of the origin of a complaint which is usually local from a general or constitutional disease." In his report Moxon stated that a similar type of case was observed by Romberg.

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Gowers² stated that "hemorrhage into the nerve sheath or Fallopian canal is a rare cause. Fracture of the skull has been thought to cause facial paralysis by this mechanism, but the nerve can scarcely escape direct damage from an injury causing hemorrhage. There are cases in which facial paralysis comes on in a few minutes and is at once complete, and in which there is no indication of any central disease. Such cases, of which I have seen two, can hardly be otherwise explained than by the assumption of a hemorrhage into the Fallopian canal, at once arresting, by its pressure, the conducting power of the fibres. This is not altogether hypothetical, hemorrhage into the canal has been found after death." Oppenheim³ mentioned briefly that "hemorrhage in the aqueduct of Fallopius gives rise to paralysis." This statement was made in connection with trauma, and it is not clear whether Oppenheim referred to spontaneous arterial rupture within the facial canal. In a series of 81 cases of malignant hypertension Keith et al⁴ observed that "paralysis of a single nerve was rare, that of the facial nerve occurring twice, and of the abducens once." In one case, a girl of 15 years, with a blood pressure of 280 mm Hg systolic and 150 mm Hg diastolic, developed a peripheral paralysis after physical exertion. Amberg⁵ noted two other cases in children.

Etienne May⁶ presented two cases of chronic nephritis in the course of which facial paralysis developed, and proposed the possibility of either syphilis or a neurogenic virus acting on the nerve, or the concurrence of nephropathy and superadded inflammation of the middle ear. The onset in the first of May's cases came on suddenly without prodromal symptoms, in a young individual with chronic nephritis. The second of May's cases, however, despite the associated hypertension, was unusual in that four attacks of facial paralysis occurred, each attack characterized by extreme pain within the ear and behind the ear at the attachment of the sternomastoid muscle, which developed several days before the onset of paralysis. In this second case an inflammatory agent seemed to be the likely cause of the paralysis.

In refutation of the deductions of E. May, Monier-Vinard and P. Puech⁷ published a further case with pathological proof of the production of a facial paralysis by hemorrhagic compression within the facial aqueduct.

This patient, C. B., a soldier, aged 21, developed chronic nephritis, characterized by headaches, general malaise, and edema. Frequent nosebleeds and amblyopia caused by albuminuric retinitis developed. Continuous tinnitus occurred. A sudden right peripheral facial paralysis ensued. There was no report of retroaural pain or perversion of taste. The blood pressure was 210 mm Hg systolic and 120 mm Hg diastolic.

Pathological examination was reported as follows: "The petrous pyramid was removed with care. There was no inflammation of the middle ear. Examination of the medulla showed no lesion at the level of the nucleus of the facial nerve. Sections of the intrapetrous portion of the facial canal made after decalcification of bone showed that a hemorrhage had occurred in

the bony facial canal. There was no trace of inflammation in the facial nerve."

The authors concluded that a facial paralysis in the course of chronic nephritis was not of necessity due to early or superadded infection but more likely was the consequence of a local vascular rupture similar to that produced with greater frequency in the nose, retinae, and brain.

Griffith⁸ called attention to the possibility of hemorrhage within the aqueductus Fallopi as an etiologic factor in producing a peripheral facial palsy, and described in detail the development of one case of right peripheral paralysis in malignant hypertension. In this case, however, the onset was characterized by a "sharp, stabbing pain over the mastoid process behind the right ear," which lasted two days before facial palsy was noticed on the right on arising in the morning. Despite the existence of hypertension, the blood pressure being 270 mm Hg systolic and 160 mm diastolic, considerable doubt is thrown on the possibility of hemorrhage as a causative factor because of the occurrence of pain for two days prior to the onset of paralysis. No pathological report was obtained in this case.

Recently this very problem was discussed by Gallavardin⁹ who failed to note the above earlier pathological observations of Moxon, and of Monier-Vinard and Puech. He stated that since both hypertension and peripheral facial palsies are common disorders, the mere occurrence of a facial paralysis in hypertensive individuals is no proof of a hemorrhagic causal factor. Seven cases were presented, all of which revealed none of the characteristics commonly found in the usual Bell's palsy. There was no retroaural pain nor perversion of taste. All seven cases were sudden in onset. The conclusion was drawn that more reports of this nature would have to be published, possibly referring to pathological proof of the possibility of its occurrence.

If Gallavardin had been aware of the two autopsied cases of proved intra-fallopian hemorrhage, he would not have been so skeptical of postulating hemorrhage as a cause of peripheral facial paralysis.

CASE REPORTS

Case 1 J. D., male, aged 54, on April 20, 1930, developed a left facial palsy overnight, noticed after a night's sleep. There were no associated symptoms. Two months previously buzzing in the left ear was first noticed which occurred periodically and had become worse lately. There was a left peripheral facial paralysis. The blood pressure was 206 mm Hg systolic and 100 mm Hg diastolic.

Case 2 R. M., female, aged 10, was admitted because of headaches, impairment of vision, in September 1937. There was a right peripheral facial paralysis. Bilateral choked discs of an advanced degree were found. The blood pressure was 268 mm Hg systolic and 140 mm Hg diastolic.

Case 3 M. K., female, aged 54, was admitted to the hospital because of a paralysis of the right face. Three weeks previously the patient experienced a mild cold. Six days before admission the right face suddenly became paralyzed. There were no other complaints. On examination there was a complete right peripheral facial palsy. The blood pressure was 248 mm Hg systolic and 120 mm Hg diastolic. Marked cardiac hypertrophy and evidences of peripheral vascular disease were found.

Case 4 M M, female, aged 65, was admitted to the hospital in May 1927 with a complaint of dizziness and headaches. The blood pressure readings were systolic in mm Hg 236, 216, 248, and diastolic 120, all readings. In August 1927 she was seen because of a facial paralysis of sudden onset seven weeks previously. There were no other symptoms or findings except a blood pressure of 210 mm Hg systolic and 118 mm diastolic.

Case 5 L L, female, aged 73, was admitted because of a right peripheral facial paralysis. Blood pressure was 150 mm Hg systolic and 120 mm Hg diastolic. At onset the patient had tinnitus in the right ear. She recovered.

Case 6 E B, female, aged 53, was seized with a severe pain about the right eye in May 1930. She had a feeling of numbness, felt dizzy, and was quite apprehensive. For two days she had a very severe headache. She felt numb about the nose and mouth. There was no disturbance of taste. Right peripheral facial paralysis was complete. The blood pressure was 230 mm Hg systolic and 130 mm diastolic. The patient recovered from the paralysis.

Case 7 G S, female, aged 42, was treated for nephritis. The left side of her face felt numb when her hair was brushed. A left peripheral facial paralysis was noted, without other complaints. The blood pressure was 235 mm Hg systolic and 140 mm Hg diastolic.

Case 8 A E, female, aged 51, in 1930 noticed sudden weakness of the right face, the left face felt as if drawn to the left. There were no other symptoms. The blood pressure was 210 mm Hg systolic. The patient stated that there had been three other attacks of the same nature.

Case 9 A F, female, aged 57, was recovering from a right hemiplegia. Six months following this she developed a sudden paralysis of the left face. The blood pressure was 190 mm Hg systolic and 120 mm Hg diastolic. The left face recovered, at which time the residual supranuclear facial palsy on the right, by contrast, was much more marked.

Case 10 M L, whose blood pressure was 200 mm Hg systolic, developed a sudden paralysis of the right face. There were no other symptoms.

Case 11 A P, male, aged 64. Twenty-five years previously a right peripheral facial paralysis occurred. In October 1937 a left peripheral paralysis very sudden in onset occurred. The previously paralyzed face was slightly contracted. The blood pressure was 180 mm Hg systolic and 100 mm Hg diastolic.

Case 12 J L, female, aged 50, had been treated for high blood pressure for seven years. In February 1940 she felt sleepy and took a nap. On awakening she discovered the paralysis of the left face. Left face felt swollen, and there was a bruised feeling in the left cheek. Taste was not disturbed. There was a complete left peripheral facial paralysis. The blood pressure was 238 mm Hg systolic and 134 mm diastolic, 225 mm Hg systolic and 130 mm diastolic.

Case 13 B Z, male, aged 49, was examined on November 12, 1935, because of a left facial paralysis, which had developed suddenly six weeks previously. There were no subjective or objective taste disturbances. One year previously a weakness of the right arm occurred with fairly prompt recovery. A complete left peripheral facial paralysis was found. The blood pressure was 270 mm Hg systolic and 150 mm Hg diastolic. The patient died six months later of a cerebral hemorrhage. No post-mortem examination was obtained.

Case 14 I S, female, aged 60, was suddenly seized with a paralysis of the left face. There were no other symptoms. Physical examination revealed a complete left facial paralysis. The systolic blood pressure was 210 mm Hg.

Case 15 M D, female, aged 48, stated that she was aware of her high blood pressure, and that she had had a stroke on the left side from which she had recovered. She came to the hospital feeling that she had had another stroke because of the sudden onset of weakness of the right face. Her face felt swollen. There was no pain.

There was no subjective loss of taste. Objectively taste was lost. Blood pressure was 200 mm Hg systolic and 120 mm diastolic.

Case 16 J M, male, aged 59, a hospital employee working in the ice plant, was known to be hypertensive. He suffered from hypertensive heart disease. Preceding the sudden onset of the facial paralysis in August 1937 he had not felt well for a four day period. The blood pressure ranged from 160 mm Hg systolic and 100 mm diastolic to 200 mm systolic and 105 mm diastolic. There were no other associated symptoms. There was no pain nor perversion of taste. The paralysis disappeared. In 1937 his blood pressure reading was 240 mm Hg systolic and 138 mm diastolic.

TABLE I
Age of Onset (Hypertensive Group) Decades *

	5th	6th	7th	8th	Total
Female	4	6	2	1	14
Male	1	2			3
					17

* One child (girl) at 10 years

Age of Onset (Inflammatory Group) Decades *

	1st	2nd	3rd	4th	5th	6th	7th	8th
Female	11	31	33	30	29	11	5	
Male	9	21	38	28	15	19	7	1

* One male @ 84, three males over 70

COMMENT

In the 16 cases the ages varied from 10 to 73 years (table 1). Except for the occurrence of one case in a child of 10 years with malignant hypertension, all cases, as might be anticipated, developed after 40 years of age. In contrast, 68 per cent of inflammatory facial paralysis occurs before 40 years of age. Peculiarly, 11 of the 16 patients (73 per cent) were females, whereas in the acute rheumatic type only 56 per cent were of this sex. Although a story of exposure to cold, sleeping in a draught, may be obtained in the so-called "refrigeration" facial paralysis, no such story is elicited in the hypertensive group, although one patient suffering from hypertensive heart disease was employed as an ice man. With the exception of his complaint the victim of the usual Bell's palsy is invariably a well person, whereas by contrast the patient suffering from hypertensive facial paralysis presents other physical evidences of vascular disease aside from the hypertension.

The average systolic pressure was 218 mm Hg, ranging from 150 to 270 mm Hg, the average diastolic pressure was 124 mm Hg, ranging from 100 to 150 mm Hg. In all cases the onset of the paralysis was sudden. In no case was there pre- or post-auricular pain or perverted sensation of taste. The associated symptoms which occurred could readily be explained on the basis of hypertensive vascular disease such as attacks of vertigo, periodic tinnitus, headache and impairment of vision. Three of the patients had had

previous cerebral vascular rupture, resulting in paralytic disturbances with recovery, and one other patient died as the result of cerebral hemorrhage, but postmortem examination was refused. Three previous attacks of facial paralysis were noted by one patient, with fairly prompt recovery. One patient experienced, 25 years previously, a typical Bell's palsy of the opposite facial nerve. Recurrences of facial paralysis are fairly common, being 5.7 per cent from all causes and 6.4 per cent in the acute rheumatic or Bell's type.¹⁰

The following cases, despite the coexisting hypertension, are more properly listed as a "Bell's palsy." The preceding symptoms of perverted taste, gradually developing weakness, and existence of pain are very common in the acute infectious, "rheumatic" or "refrigeration" type of peripheral facial paralysis. Where these symptoms precede the onset of paralysis and are severe, the case cannot be considered to be caused by hemorrhage.

CASE REPORTS

Case 1 H. H., female, aged 48, felt mild pain behind the left ear on October 27, 1937. On October 30 the facial paralysis was noted about the mouth, and a sense of fullness in the left ear. Blood pressure at this time was 190 mm Hg systolic and 128 mm Hg diastolic.

Case 2 A. H., female, aged 54, developed severe pains back of the neck and the right shoulder. Four hours after onset the right eye could not be closed. The right face was completely paralyzed the following morning. A brassy taste in the mouth was noted before the facial paralysis developed. Sense of taste was lost. The patient was very sensitive to loud sounds. One month previously a severe headache on arising, lasting several hours, was noted. The blood pressure was 210 mm Hg systolic at this time.

Case 3 M. M., female, aged 45, was known to have had a high blood pressure for two years. On April 5, 1938, she complained of pain over the right mastoid. She thought she was getting an earache and was advised by the family physician to rub olive oil on it. The paralysis of the right side of the face came on suddenly. There was a severe disturbance of taste, like acid or aluminum. There was a complete right peripheral facial paralysis. Taste was lost on the right half of the tongue. The blood pressure was 240 mm Hg systolic and 144 mm diastolic.

Case 4 E. C., female, aged 50, had been a known hypertensive for years. Blood pressure was 164 mm Hg systolic and 114 mm diastolic, for which she was receiving treatment. On June 7, 1940, pain developed behind the right ear. The next day the left face suddenly became paralyzed. There was no subjective or tested loss of taste. Blood pressure at this time was 160 mm Hg systolic and 120 mm diastolic.

Case 5 M. D., male, aged 28, in August 1939 after sleeping at night with all windows open, awakened with a paralysis of the right face. Food tasted differently on the right side. The right ear seemed much more sensitive to sound. The patient had been treated for kidney trouble. After the onset there was slight pain over the right forehead, cheek, and behind the right ear. There was a complete right peripheral facial paralysis. Blood pressure was 190 mm Hg systolic and 140 mm diastolic.

Case 6 C. B., female, aged 58, on August 23, 1938, noticed a paralysis of the right half of the face on awakening in the morning. The patient complained of a loss of taste on the right half of the tongue. No pain was noticed. There was a complete right peripheral facial paralysis. Sugar was tasted on the left but not on the right half of the tongue. The blood pressure was 170 mm Hg systolic and 104 mm diastolic. Advanced retinal arteriosclerosis was present.

COMMENT

Despite the coexistence of hypertension, the symptoms of preexisting postauricular pain, subjective perversion of taste, objective loss of taste, gradual development of facial paralysis are found to occur much more frequently in the common Bell's palsy, "refrigeration" or "rheumatic" type of facial paralysis, and the above six cases are so regarded

DISCUSSION

An isolated facial palsy, sudden in onset, possessing all of the characteristics of a paralysis of true peripheral origin would seemingly not be confused with a supratentorial lesion. Even if there should be exception to the traditional anatomic concept of bilateral cortical innervation of the occipito frontalis muscle, it is inconceivable that a hemorrhagic insult in a known hypertensive individual should be discreetly limited to the cortical facial center. The same reason applies to the pseudoperipheral facial paralysis of Friedman, as neighborhood signs should invariably be present.

Similarly, in the brain stem vascular damage sufficient to produce a complete peripheral facial palsy should be associated with a sixth cranial nerve palsy and involvement of the adjacent descending and ascending long tracts, assuming the patient survives bleeding in this location. Because of the not unusual occurrence of an abducens palsy in hypertensive vascular disease, explained by pressure from crossing arteries, there exists the theoretical consideration of a similar aneurysmoid disturbance of the internal auditory in the cerebellopontine angle. The evidence would indicate that instead of the production of a facial paralysis, the nerve is likely to be relatively undisturbed. For it is a matter of common observation that severe dislocation of the facial nerve with little or no evidence of paralysis manifested on physical examination is found in instances of tumor of the eighth nerve, and also in distortions of the accompanying auditory artery in certain occurrences of paroxysmal vertigo. However, when a peripheral facial paralysis is observed in such situations, there is a story of slow development as well as a severe involvement of the adjacent eighth nerve. Above all it is extremely unlikely that the seventh nerve alone would be implicated in this location by compression by the neighboring vessels. On the other hand the two quoted cases of proved hemorrhage show that bleeding within the facial aqueduct can cause a sudden isolated peripheral facial paralysis.

The blood supply of the internal ear and the Fallopian canal is derived from three sources, from the basilar artery by way of the internal auditory artery, from the middle meningeal artery by way of the petrosal artery, and from the posterior auricular artery through the stylomastoid artery.

The internal auditory artery (a. *auditiva interna*), a long slender branch, arises from near the middle of the basilar artery, it accompanies the corresponding auditory nerve into the internal auditory meatus and is distributed to the internal ear. The stylomastoid artery (a. *stylomastoidea*)

enters the stylomastoid foramen, in relation to the facial nerve, and supplies the tympanic cavity, mastoid cells and semicircular canals. It is carried onward in the Fallopian canal to anastomose with the petrosal branch of the middle meningeal artery. According to Politzer¹¹ this artery, which runs practically throughout the whole length of the canal, supplies the neurilemma of the facial nerve. A branch of the middle meningeal artery called the *petrosal artery* (*ramus petrosus superficialis*) enters the hiatus Fallopii (*hiatus canalis facialis*), supplies the facial nerve (*vasa nervorum*), and anastomoses with the stylomastoid branch of the posterior auricular artery.

Hemorrhage from the internal auditory artery is not likely to cause an isolated peripheral facial paralysis. It is intimately associated with the auditory portion of the eighth nerve as it is about to enter the internal auditory foramen. A vascular accident at this point would not solely compress the facial nerve, but also would induce the picture of spontaneous subarachnoid hemorrhage. In addition, the interruption of blood supply to the internal ear would logically bring about labyrinthine signs and symptoms.

Bleeding from the stylomastoid artery as it courses with the facial nerve could compress the trunk of the facial nerve and induce a paralysis. Part of its course lies below the point at which the chorda tympani nerve joins the facial nerve, and since some of the cases of facial paralysis have an associated loss of taste on the corresponding half of the tongue, bleeding from the artery at its point of entrance would not account for all cases of facial paralysis on the basis of hemorrhage.

A likely source of hemorrhage compressing the facial nerve is the petrosal artery. This vessel enters the upper limits of the facial canal at its constricted portion. Interruption of taste fibers could occur at this locus. The interference with blood supply from this vessel would also disrupt the circulation to the facial nerve trunk, supplied by *vasa nervorum* arising from the petrosal artery. This concept is supported by the location of the hemorrhage in both Moxon's case, and that of Monier-Vinard and Puech.

Hemorrhage from or traction on the petrosal artery might possibly be the causative factor in producing the peripheral facial paralysis observed after operative approach to section of the posterior root. The commonly accepted theory, first proposed by Alfred Taylor, is that traction on the greater superficial petrosal nerve running in the peeled up dura caused swelling in the geniculate ganglion of the facial nerve. The swelling of this ganglion in turn compressed the adjacent motor trunk of the seventh nerve. If traction is responsible for the paralysis, is not the more direct connection of the meningeal artery with the motor root of the seventh nerve by way of the petrosal artery equally responsible, or is it possible that bleeding within the facial aqueduct can be produced by traction with subsequent laceration of the vessel and bleeding?

In malignant hypertension bleeding from small arterial twigs is common, the main pathologic changes being in the small arteries and arterioles.

Repeated nosebleeds, conjunctival and small retinal hemorrhages are not unusual. Bleeding from small arterial vessels of slightly greater caliber within the facial canal should not meet with scepticism, since there is adequate postmortem proof of such occurrence.

To postulate hemorrhage as a cause of facial paralysis the onset must be sudden, as is true of hemorrhages in vascular rupture elsewhere in the nervous system. There is no preliminary pain or disturbances of taste. The patient may have had previous attacks of hemiplegia, or suffered from dizzy spells or headaches, or have been treated for existing vascular hypertension. The coexistence of high blood pressure with such onset should arouse suspicion of the possibility of aqueductal hemorrhage rather than inflammation as the cause of the paralysis.

On the other hand, the occurrence of pain, muscular twitchings, or perverted sense of taste antedating the onset of paralysis indicates a slowly acting etiologic agent, probably inflammatory. Pain is of varying intensity and of varying distribution and is found commonly in ordinary Bell's palsy. Contrary to the expressed opinion its presence is to be regarded as the rule rather than the exception. In some instances pain is recalled only by direct questioning, although in many cases it is volunteered. The most common site of pain is directly over the mastoid process on the affected side. A spread to the shoulder, neck and face is noted in some cases. If there is severe pain within the ear, herpetic facial paralysis of Ramsay Hunt must be considered. The pain may antedate the paralysis several days or may be first perceived at the time of or after the paralysis is first noted. Perversion of taste, disagreeable at times, precedes the onset of paralysis with a fair degree of frequency. About in the same proportion are those patients in whom taste is found to be lost on testing on the affected side without subjective awareness. Despite the coexistence of hypertension, the presence of the above symptoms antedating a paralysis does not favor the hypothesis of hemorrhage into the facial aqueduct (table 2).

TABLE II
Contrasting Features

	Bell's Palsy	Hypertensive
Age, per cent	Young adults, 68 per cent before 40	Higher decades (after 40)
Perversion of taste	Present, antedating paralysis	Absent
Pain	Retroaural (common) antedating paralysis	Absent
Onset	Frequently gradual	Always precipitate
Recurrence	Tendency of 6-4 per cent	No recurrence on hypertensive basis
Associated physical signs	None	Vascular hypertension, arteriosclerosis
Significant history	Absent	Previous headache, vertigo or bleeding elsewhere, brain, retinae

CONCLUSION

Sixteen cases of hypertensive peripheral facial paralysis are presented. In all cases there was a precipitate onset without antecedent retroaural pain or perversion of taste. The incidence is 3.7 per cent for all causes of facial paralysis.

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HAS A REAL INCREASE IN LUNG CANCER BEEN PROVED? ¹

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IN the last two decades, an enormous amount of literature has appeared on the clinical, pathological and etiological aspects of lung cancer. One of the most important stimulants to the finding of supposed causes of lung cancer in the environment has been its alleged *real* increase. Although not all workers have accepted this idea, the majority have considered that this disease has increased in a real way and that the increase cannot be attributed wholly to advancing age of the population, to better diagnosis, or to the growing interest of the medical profession in the disease. The literature will not be reviewed, as it has been well covered in such monographs on lung cancer as those of Simons and of Fried, among others.

METHODS OF MEASURING "INCREASE" IN A DISEASE

Because some of the thinking on the question of increase in lung cancer has not been particularly clear, let us go into the matter of what we mean by an increase in a disease. We have two yardsticks by which we can measure "increase" in a disease, and we must be sure of which yardstick we are speaking and what each measure is able to tell us about the behavior of a disease. First, there is the "incidence" yardstick, by which we may determine (a) the morbidity rate of a disease, or (b) the mortality rate of a disease. In some instances these two will differ widely, as for example in measles, but in lung cancer the two rates will correspond rather closely. Second, there is the "ratio" yardstick, by which we measure the ratio between deaths due to the disease in question and the total number of deaths. It may be that a disease is increasing according to both measures, it may be decreasing according to both, it may be increasing by one and decreasing by the other, or it may be remaining stationary by one, and either increasing or decreasing by the other. Its incidence in the population usually is measured in terms of the number of deaths it causes per 100,000 of the population, and unless a small specified age and sex group is being considered as the standard, the death rate of a disease may be as much influenced by the birth rate, as by the actual number of those dying from the disease. In this discussion, however, I will assume that when I speak of the incidence rate, I am speaking of the death rate not in the entire population but in a small limited group of defined age and sex distribution. It will also be noted that the ratio measure is as much influenced by the behavior of other diseases as by the behavior of the disease being studied. I will discuss that later. When I state that a disease is increasing I must define the measure I am

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using, and must understand just what each measure is able to tell me about the behavior of the disease

For the moment I am going to dispense with the fact that not all diseases are properly diagnosed. I will assume for my illustration that all diseases occur with equal frequency in all age and sex groups. Let us now look at figure 1, a. Here the white block represents all deaths from dis-

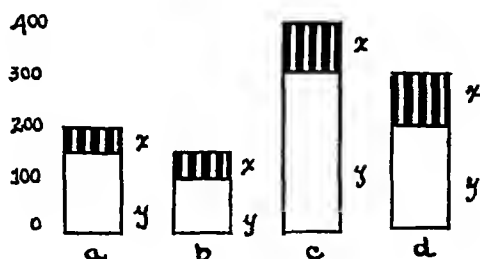


FIG 1

eases other than those from x , which we have shown as the black barred area. All these diseases together we will call y . I have chosen to make x responsible for 25 per cent of all deaths, y responsible for 75 per cent. The death rates I have set as 50 per 100,000 for x , and 150 for y . In b , c and d I have represented three later periods of time than that shown in a , and have chosen to make the deaths from the diseases x and y behave differently in the three periods. In b , owing to the elimination of infectious diseases to a large extent, deaths in the population decrease in proportion to the number of those living, so that the death rate from y is now 100 instead of 150, and from x plus y 150 instead of 200. But the death rate from x has remained the same, namely 50, so that by the incidence yardstick, x is remaining stationary. By the ratio measure it has increased, for it now is responsible for $33\frac{1}{3}$ per cent in place of 25 as in a . Although not causing any more people in the population to die in proportion to those living, it has increased in importance as a cause of death, since more of those who die, have to die from x than died formerly. Its increase has been a relative, but not an absolute one.

I will now choose to have x increase absolutely but not relatively. In rectangle c all deaths have doubled, so that the death rate from y is now 300 in place of 150 as in a , and from x 100 in place of 50. Twice as many of the population are dying as died in a , and twice as many are dying of x as died in a . But x still continues to be responsible for 25 per cent of the deaths in the population.

Finally, as shown in d , x has increased both relatively and absolutely. The total death rate has increased to 300 in place of 200 as in a , the death rate from y has jumped from 150 to 200, and that from x from 50 to 100. x has increased 100 per cent by the "incidence" yardstick, but has increased only $33\frac{1}{3}$ per cent by the ratio yardstick. Deaths from y , although they in-

creased absolutely from 150 to 200 in 100,000 of the population, have decreased relatively, having dropped from 75 per cent in *a* to $66\frac{2}{3}$ per cent in *d*

Throughout, I have assumed that all deaths were adequately diagnosed, so that none escaped recognition. Unfortunately, however, we do not live in a world in which this ideal is attained. There remains in every disease, and particularly in diseases like lung cancer in which the identification tag is not displayed externally as it is in scarlet fever or in lip cancer for example, an unidentified residue which may be greater numerically than the group of cases which are correctly diagnosed. We have no way of knowing the proportion of the total which the unrecognized group forms. If we had it would no longer be an unrecognized group. We cannot even hazard a guess, for the autopsied group forms an almost negligible part of those that are dying, hence, any guess based upon the assumption that this small sample is representative of the total population is bound to be erroneous. We do not know whether the incidence of lung cancer is increasing, the most we can do is to observe the fluctuation in the incidence of *diagnosed* lung cancer cases. These may be and probably are two quite different values.

THE IMPORTANCE OF THE UNRECOGNIZED CASES

Let us see how diagnosed cases of a disease can increase both relatively and absolutely, and in such striking fashion as to convince us that it must be a real increase, without there being any increase in the actual cases of the disease or alteration in the ratio of total deaths which it causes. Of course, I must make a purely hypothetical case and I have no way of knowing that this is what actually happens in lung cancer. The illustration is merely designed to show that with an unchanging incidence of the disease, an *appearance of increase* can be attained. In figure 2 are shown three

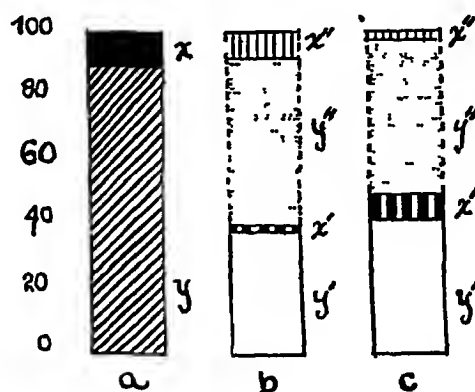


FIG 2

blocks. In *a*, I have represented the proportions of *x* and *y* as 10 per cent and 90 per cent of the total deaths. This is the true state of affairs in the hypothetical population based upon the percentages which would be present if all cases were autopsied. In *b* and *c* are represented two periods of time

such as 1900 and 1930, in which for the purposes of illustration I have assumed that x and y are still causing 10 and 90 per cent of the deaths respectively, and in which the incidence of the diseases in the population has not increased at all, as shown by the total heights of the columns being the same as in a . But here the accurately diagnosed cases coming to autopsy are shown as x' and y' , and it is seen that they do not by any means form the majority of the cases of disease in the population. I am assuming that I know the proportions of unrecognized cases in this illustration which, of course, is impossible in real life. The unrecognized cases of y' are designated as y'' , and of x' as x'' . Now x' plus x'' equals x in the first rectangle a , and y' plus y'' equals y as in a . Neither disease has increased either relatively or absolutely in the interval between b and c .

The death rates from the diseases have been set as 10 and 90 per 100,000, if all cases were diagnosed at autopsy. But because they were not, in b , the *recognized* death rate from y' was 38 per 100,000 in place of 90, and the *recognized* death rate from x' was 2 in place of 10. The deaths due to x' were 5 per cent of all autopsied deaths and from y' were 95 per cent. The deaths in this period which are designated as x'' and y'' may have been called senility deaths, a dump heap for all deaths in old age in which the physician could not make a diagnosis. Now in period c , which is later than b , there has been improvement in diagnosis, and fewer deaths have gone into the miscellaneous heap shown in the upper part of the diagrams b and c , and more have moved down into the clear white and the heavily barred areas. Because the disease x was one which was internal and hard to recognize without the modern means of diagnosis, and because y contained a great many diseases which were external and in which improvement in diagnosis, therefore, had not been so spectacular as in x , the section x' in c has grown faster than y' as compared with their values in b . That means that less of the residue x'' remains at the top of the diagram than was there in b .

The death rate from y' has grown from 38 to 42, and that from x' from 2 to 8, so there has been a tremendous absolute increase in x' from b to c . There has been also a relative increase in x' , for whereas it formed but 5 per cent of autopsied deaths in b , it now forms 16 per cent in c . y' has also increased absolutely from 38 to 42 per 100,000, but has decreased relatively, dropping from 95 to 84 per cent of all autopsied deaths. When we look at the top sections of b and c , however, we find that the sum of the autopsied and unautopsied cases of x and of y form exactly the same percentages as in a , and that there has been no increase in either disease in the interval between b and c . Looking at only the autopsied cases we are convinced that the incidence of x has increased both relatively and absolutely.

Now let us apply this hypothetical example to lung cancer. We see from examining the data culled from the literature on the increase of lung cancer that they are of necessity data which relate only to the bottom of diagrams b and c , that is, the autopsied cases. All those cases which lie at the top of these two rectangles in the unknown section x'' and y'' must of necessity be

omitted from their calculations. Whether in real life the sum of x' and x'' of 1900 is the same as the sum of x' and x'' in 1930 we have no way of knowing, for we do not know the value of x'' in either period. We cannot guess what it is, because the total autopsies are too small a part of all deaths to be an adequate sample. What observers have been studying is the increase in recognized lung cancer cases in relation to other forms of recognized cancer, and they have assumed that their conclusions apply to all cases of lung cancer. Thus, from evidence such as that contained in the lower sections of b and c , labelled x' and y' , workers have deduced that they knew about x and y as they actually existed in a . Simons, for example, states "It is apparent that the evidence permits of no other conclusions than these first, that incidence of the disease has increased both absolutely and relatively, second, that continued suggestions that such an increase is only apparent and not real, are rebuked by the facts." I point out that the evidence does not permit of such conclusions, at least not to a critical thinker. Because we do not know how many general cancer cases lay in the upper dotted portions of the rectangle in the earlier period and do not know how many lie there today, because we cannot even hazard a guess as to how many lung cancer cases were in the upper lightly barred area then or how many are there now, we are wholly incapable of saying that the incidence of lung cancer has increased either relatively or absolutely, or both. The most that we can say is that *diagnosed* cases of lung cancer are *probably* showing both a relative and an absolute increase over the diagnosed cases of lung cancer one or two decades ago. Since no one would be rash enough to claim that the small percentage of autopsies performed reflect accurately the percentages of various diseases as they occur in the population, either in earlier times or now, no one can justifiably state that the data based on autopsy statistics indicate trends in incidence of actual lung cancer cases. Indeed, Wells has said that if one were to judge by autopsy statistics, skin cancer would be rare and internal cancers common.

As long as we do not know the data hidden in the upper part of the two rectangles, b and c , so long must we refrain from drawing any conclusion as to the incidence of lung cancer. We must confine our speculations entirely to *diagnosed* lung cancer. It may be that the conclusions for the two would run parallel, but we have no way of knowing that that is the truth while such a negligible portion of the population comes to autopsy, since obtaining an autopsy depends so largely upon the eagerness of the attending physician to have his diagnosis verified or clarified.

I said a few moments ago that the most we could do was to conclude that diagnosed cases of lung cancer were *probably* increasing. I used the word "probably" advisedly, because the data upon which Simons and many other authors base their conclusions have not been adequately analyzed to permit of these conclusions being certain even for *diagnosed* lung cancer cases. Let us look at some of the most obvious fallacies in the methods employed to determine this so-called increase of lung cancer cases, remember-

ing always, when I speak of lung cancer, that I mean *diagnosed* lung cancer. Any question as to an increased incidence in *actual* lung cancer cases must remain unanswered until such time as autopsies are universal, or almost so, with the result that the sample of the population occurring in the autopsy group is so large a percentage of the total population that any conclusions drawn from it cannot be far removed from the truth.

METHODS USED TO DETERMINE INCREASE IN LUNG CANCER

1 Ratio of Lung Cancer Autopsies to Total Autopsies Several means of determining the increase of lung cancer have been tried. The first was the method of ascertaining the ratio of lung cancer autopsies to total autopsies performed in a single hospital service over a period of years, and the alteration in that ratio. In most of these investigations, a marked increase in lung cancer was found. The numerous citations dealing with this aspect can be found in most of the recent monographs on lung cancer (Fried, Simons, etc.)

Fallacies of the Method It was soon realized, however, that this method contained a great many fallacies, the most obvious among them being that of possible *dissimilarity of age* in the two autopsy groups under consideration. Because of the increasing age of the population in general, it would probably be true that the average age of patients coming to autopsy had increased in recent years, and since most cases of lung cancer occur in middle age, more cases would be likely to be found in the later autopsy groups than in the earlier. This dissimilarity in age was compensated for to some extent by limiting the general autopsies to those done on adults only, past the age of 20. This was not sufficient, however, because lung cancer is not uniformly distributed throughout adult life, but increases definitely up to the age of 60, and may even increase after that.

A second fallacy inherent in this method of estimating a possible increase in lung cancer, and one which cannot be compensated for, is that only a small fraction of hospital patients come to autopsy in many hospitals, and even if the autopsy rate be high in the hospitals, only a small fraction of the total population in a community comes to autopsy. The ratio of lung cancer autopsies to total autopsies may, therefore, give no true picture of the *actual percentages of the population affected with lung cancer* in either the earlier or later periods, which are the percentages we wish to know.

A third fallacy inherent in this method is one which has to do with the physician's desire to verify a diagnosis, or to find a cause of death when diagnosis has been impossible. If a case is supposedly clear cut, with all agreeing on the diagnosis, and if the disease from which the patient has been supposedly suffering is one which is common, then the patient is not likely to come to autopsy. In the earlier years, when a patient had a cough, with sputum, fever, loss of weight, etc., the diagnosis of tuberculosis was most likely to be made. Tuberculosis was a common disease. There might be

no great desire on the part of the physician or the family to have an autopsy to verify a diagnosis of which everyone felt confident. Today, although tuberculosis would still be the diagnosis in some of these cases, the failure to find tubercle bacilli in the sputum and the realization that lung cancer is fairly common might lead the physician to ask for an autopsy to confirm his suspicions. There might, therefore, be a higher percentage of lung cancers found at autopsy today than was formerly the case without lung cancer being actually more prevalent now than then.

A fourth fallacy common to all the methods used is that we can not be sure that the standard against which we measure the increase of lung cancer remains constant. As Hill points out in his book on Medical Statistics, a ratio can be changed by altering the denominator of the fraction as well as by altering the numerator, a fact which appears to be overlooked by most of those who conclude that there can be no doubt that lung cancer has undergone a real increase, because it forms so much larger percentage of all autopsies, or of all cancer autopsies now than it did 20 or 30 years ago.

Let us take a very simple illustration of this point. In a field there are 25 horses, 20 of them black, five of them white. The ratio of white to black is $\frac{5}{20}$ or $\frac{1}{4}$. Now that ratio can be increased in two ways. I can put more white horses in the field, thus increasing the total number of horses as well as the percentage of white horses, or I can take some of the black horses out, decreasing the total but increasing the percentage of white horses. Thus I can add five white horses so that the ratio becomes $\frac{10}{20}$ or $\frac{1}{2}$. I can take away 10 black horses, and have $\frac{5}{10}$ or $\frac{1}{2}$. The alteration in the denominator of a fraction may be responsible for the alteration in the ratio, just as much as the alteration in the numerator.

As illustrative of this point, suppose I consider a hypothetical hospital with its autopsy records. Thirty years ago there would have been a large number of autopsies on cases dying of infectious diseases. Today that number would be materially lessened. Also, although the population in the district has doubled in the period of 30 years, the hospital beds may not have doubled, so that the number of patients accommodated during each year has remained more or less stationary. None of the diseases has increased in the district, but because there are fewer acutely ill patients from infectious diseases there are more beds available for the more chronically ill, so that a higher proportion of those with such diseases find their way into the hospital, and hence into its autopsy records. I will set forth these data in a table, to show how lung cancer may actually increase by 100 per cent in autopsy records, without there being any real increase and with the only explanation

	Autopsies due to infectious diseases	Cardio-vascular	All other cancers	Lung cancer	Total
Period a	700	150	100	50	1000
Period b	400	300	200	100	1000

being a decrease in some other disease. Thus, I am not allowing for age change in the population, nor for better diagnosis, nor for more interest in the subject of lung cancer, I have merely made beds available for lung cancer cases by clearing out the infectious diseases.

Here there was a total of 1000 autopsies in each period. Because the population in the district had doubled, there were twice as many heart cases, twice as many cancers, of which lung cancer shared the same percentage each time. But lung cancer was 5 per cent of the autopsies in period *a*, and was 10 per cent in period *b*. Here there has been a relative increase in lung cancer among the autopsy group, not because more people are actually dying of it in proportion to the population, but because fewer people are dying of infectious diseases.

A factor which will probably increase the percentage of lung cancers to general autopsies, even with age, sex, and all other factors compensated for which are capable of being compensated, is the new treatment of pneumonia. Many hospital deaths and many autopsies were of pneumonia patients. Now that specific therapy is materially lessening the death rate and hence the probable numbers of autopsies from this cause, lung cancer will show an increase, not necessarily because more are dying of lung cancer, but because fewer are dying of something else. Since the percentage of deaths due to different diseases must always total 100, a decrease in any one percentage automatically raises all the other percentages, without the actual number of deaths being altered at all. This is clearly brought out in figure 1, *a* and *b*.

2 Ratio of Lung Cancer Autopsies to All Cancer Autopsies It was realized that there were many objections to comparing lung autopsies with all autopsies, and hence many writers began to compare the lung cancer autopsies with all cancer autopsies, to see if lung cancer were increasing more rapidly than cancer in general.

Fallacies of This Method At the outset it may be said that practically all of the objections which can be brought against the first method can be brought against this one also. It is true that there is not likely to be so much age shift in the general cancer groups in the two periods compared as there might be in general autopsies. But the second objection still has force, namely, that the proportion in which cancers come to autopsy may be far from representative of the proportions in which they occur in the general population. Third, the physician may not be anxious to verify a diagnosis of breast cancer or of lip cancer which is quite obvious even to the naked eye, whereas he may be anxious to have clarified the symptoms of lung cancer in an obscure case. The fourth objection, that the standard against which we are comparing lung cancer may be a shifting one, is perhaps as potent as any. The denominator of the fraction, namely, cancer autopsies may be one that is shifting, altering the value of the ratio, rather than that lung cancer is altering.

a Effect of improved therapy in other cancers on lung cancer increase
Because this point is so seldom discussed or even mentioned in the studies which deal with the supposed increase in lung cancer, I am going into this a little more fully I will construct a hypothetical series to bring out the method in which lung cancer can appear to be increasing without actually doing so I am not trying to prove that diagnosed lung cancer is *not* increasing but am merely asking "Have the data which have been used in support of this idea been critically examined to show the real relationships?" Again *a* and *b* are the two periods of time under investigation The population which is middle-aged and which might develop any cancer has just doubled in that interval Therefore, the finding of twice as many cancers in the period *b* will not indicate any increase in actual percentage of population showing cancer I shall assume that I know just how many actual cancer cases there were at any time whether they were properly diagnosed or not Now I shall put these hypothetical figures into a table

Period *a* Total population of middle aged persons—1000

Total no of cancer cases—100		Total no recognized—75 or 75%		
	Gastric ca	Rectal ca	Breast and uterine	Lung
Actual number	30	30	35	5
No recognized at autopsy	20	25	28	2
% of autopsied ca cases in each group	26 6%	33 3%	37 3%	2 6%

Period *b* Total population of middle aged persons—2000

Total no of cancer cases—200		Total no recognized—150 or 75%		
	Gastric ca	Rectal ca	Breast and uterine	Lung
Actual number	60	60	70	10
Ca cases proved by autopsy, biopsy or surgical specimen	40	50	56	4
No coming to autopsy	24	30	32	4
Percentage of autopsy cancer cases each group	26 6%	33 3%	35 5%	4 4%

Examination of these figures will show that cancer in general has not increased, because 10 per cent of the middle-aged population actually has cancer in each period Also, the actual ratios of gastric, rectal, breast, uterine and lung cancers have not changed in the two periods, since there are just twice as many of each in the latter period as in the former But I am comparing lung cancer *autopsies* to all cancer *autopsies* and whereas all the histologically proved cancer cases in the first period were actual autopsy cases, in the latter period of time many *proved* general cancer cases did not get into the autopsy records, although 100 per cent of *proved* lung cancers were autopsy cases Therefore, the denominator, cancer autopsies, *has not re-*

remained constant in the two periods of time Improvement in therapy has occurred and more surgery is undertaken on gastric and rectal cancer cases, with the result that a histological diagnosis has been made on surgical specimens from patients who did not die but recovered. If they died, the surgeon, being quite satisfied that his clinical diagnosis was correct, since it had been verified by the pathologist, did not ask for an autopsy. Breast and uterine cancer are two types which surgery and roentgen-ray are able to help to a very large extent, therefore, quite a number of these would be operated upon, a histological diagnosis would be made on the biopsy or surgical specimen, and the patients would survive. If they died, the diagnosis was quite clear, having been verified by the pathologist, the surgeon's curiosity would be satisfied and there would be even less tendency to ask for autopsies than in the cases of the gastric and rectal cancers. So, of the 150 *proved cancer cases* in the latter period *only 90 actually came to autopsy*. The lung cancer has been kept constant, there are just twice as many of them in a population twice as large. Since those that are finally diagnosed histologically are practically all done at autopsy, the *number of proved lung cancers* is the same as the *number coming to autopsy*. Although lung cancer has not increased in this example, either through being diagnosed more often, or through increased age of the population, it has shown an increase in the percentage it forms of all cancer autopsies, because the denominator of the fraction, namely, the percentage of all cancers diagnosed which came to autopsy, has changed.

This is, of course, purely hypothetical, but it serves to illustrate very well the point that according to the figures lung cancer increased from 2.6 to 4.4 per cent in this time, an increase of 69.2 per cent for lung cancer. Since the percentages of each type of cancer that came to autopsy had not increased at all in our example, lung cancer would have been assumed to have shown a very marked increase.

b Effect of better diagnosis in all forms of cancer on lung cancer increase Now suppose that I allow all forms of cancer to show the effects of better diagnosis, although we still keep the proportion of different tumors the same in the two periods. Gastric and lung cancers will show a greater improvement in diagnosis than rectal, breast and uterine cancers since the latter are so obvious in their effects that improvement in diagnosis would not have been so great as in the case of gastric and lung cancer. In other words, I am going to alter the numerator as well as the denominator of the fraction

Period b	Gastric cancer	Rectal ca	Breast and uterine ca	Lung ca	Total
Actual no. cases	60	60	70	10	200
Cases proved by histological diagnosis	50	53	60	7	170
Autopsied cases	40	33	30	7	110
Percentage of each group in autopsied cases	36.3%	30%	27.2%	6.3%	

Now lung cancers are 6.3 per cent of all cancer autopsies, an increase of 142 per cent, although all cancer autopsies have increased only 46.6 per cent over what they were in period *a*. Surely that should be sufficient proof, say those who believe in the great increase in lung cancer, that lung cancer is increasing faster than cancer in general, and should silence those unbelievers who doubt that lung cancer is actually increasing¹. And yet, we know that lung cancer has not increased one iota in the latter period, it is merely that the recognized cases form a higher percentage of the total than they did in the earlier period.

c Effect of better diagnosis of lung cancer alone on lung cancer increase
Of course I can alter the numerator alone, in this hypothetical population, and have all the other cases come to autopsy in exactly the same numbers in the latter period as in the former, and let lung cancer alone show the benefit of increased value in diagnosis. What happens then? There would be, under such conditions (table 1, section 2), 40 cases of gastric cancer, 50 of rectal, 56 of breast and uterine, and seven of lung cancers in our autopsy group, in the latter period of time. There would still be a great increase of diagnosed lung cancer, an increase from 2.6 per cent to 4.6 per cent of all cancer autopsies. But again, actual lung cancer incidence would be the same in the two periods.

I have gone into this at some length, because it must be emphasized that when one is attempting to ascertain the behavior of one phenomenon, one must be sure that anything with which it is being compared remains standard during the time of comparison. If the number of gastric, rectal, skin, breast or uterine cancers, or any combination of them is shifting their percentages in the autopsied cancers during the period under investigation, then any alteration in the ratio of lung cancer autopsies to total cancer autopsies cannot legitimately be attributed to a rise or fall in the lung cancer cases alone. No one can go the length of stating that exactly the same proportion of all other types of cancers are coming to autopsy today as did 20 or 30 years ago, that they are not varying at all, and that all the alteration is due to an overwhelming increase in the lung cancer cases. We must find out what is happening to these other cases as well as to the lung cancer cases.

Thus, the workers who base their conclusions upon the circumstance that lung cancer autopsies now form a greater percentage of *total cancer autopsies* than was the case formerly seem to have ignored the following facts: (1) that now not all verified cancer cases come to autopsy. These workers should at least include in their denominator all verified cancer cases whether the diagnosis was made at autopsy or from biopsy or surgical specimens, (2) that alterations in the denominator of the ratio, caused by decreased incidence of any form of cancer, alter the value of the ratio, without there having been any necessary alteration in the lung cancer cases, (3) that improvement in the diagnosis of lung cancer may have been and no doubt is much greater than is the case with obvious forms of external cancer, such as lip, and breast, or forms which cause obvious symptoms such as rectal or uterine cancer.

Therefore, diagnosed lung cancer cases may show a relative and absolute increase without altering the incidence of the disease (figure 2 c)

Alterations in Sex Ratio in Autopsy Cases in the Two Periods The matter of sex must be brought up. Lung cancer gives evidence of being more frequent in the male. If all cancer autopsies or if all general autopsies varied in their ratio of male to female cases in the two periods under comparison, it would affect the ratio of lung cancer to total cancer cases or to total autopsies without there being of necessity any real alteration in the proportion of lung cancer cases. Let us take an example. Suppose that in the first period there were 100 cancer autopsies. Of these 40 were males and 60 were females, because breast and uterine cancer formed such a large part of the cancer autopsies of the earlier period. Of the 40 males, two had lung cancer, an incidence of 5 per cent lung cancer among males. In the later period of time, owing to the fact that the lives of many women with breast and uterine cancer were saved because they were operated upon earlier in the course of the disease or treated with radium, and owing to the fact that more males were actually coming to autopsy because of National Health Acts and Workmen's Compensation Acts which permitted wage earners to be hospitalized whereas formerly they were not, in the 200 cancer cases in the later period there might be 120 males and 80 females. If 5 per cent of male cancers were again lung cancers, we would have six lung cancer patients. These would form 3 per cent of all cancer autopsies, as compared with 2 per cent of all cancer autopsies in the first period, an apparent increase of 50 per cent in lung cancer cases.

It becomes evident, therefore, that the method of determining whether or not lung cancer is increasing, by comparing the percentage of lung cancers found among all cancer autopsies in two periods of time is one which is full of statistical pitfalls. Some of these may be avoided by separating the two sexes and determining the increase for each sex separately, and by separating the total cancer and lung cancer cases into age groups of 10 or even five year periods for determining the increase within each group.

Finally, since many cancer cases now do not come to autopsy because they have had temporary or permanent curative treatment, they should be added to the autopsy records whenever the diagnosis has been confirmed histologically. Thus, if in the intervening years between periods *a* and *b* in our hypothetical hospital there had been placed a large radium and roentgen-ray clinic, so that now many of the skin, breast and uterine cancers were cured, it would be most fallacious to compare *autopsy* records only of the two periods. Many proved cancer cases would no longer be autopsy cases.

3 Hospital Admissions as Basis for Comparison Because there have been criticisms against using all autopsy records in the two periods compared as the denominator of the fraction and because some authors have seen the fallacies which lurk almost inevitably in using even total cancer autopsies as the denominator of the fraction, it has been suggested that "total hospital admissions" be the basis of comparison. Thus a man who

was ill with lung cancer would perhaps be admitted in 1900 to a hospital as readily as today, and whether he came to autopsy or not, he would be listed in the hospital admissions

Much the same criticisms hold here. Total hospital admissions in an early period would contain many young persons; also, the sex distribution in the two periods may not be the same. As Passey and Holmes point out, in the teaching hospitals of England, in which there is not room enough for all cases applying for admission and in which selection of cases for admission is based partly upon the desirability of the patient as teaching material, such data would be almost useless. Forty years ago, a man with a chronic cough, blood-streaked sputum, etc., might not be admitted because he would be considered a chronic case of tuberculosis, a disease of which the students were seeing sufficient, whereas today he would be admitted because of the possibility of his having a lung cancer, of which the students had seen but few cases. Finally, if, as these authors point out, a new wing to the hospital has been opened, lung cancer will show an increase in the hospital records if the wing has been one for medical admissions of men, it will show a decrease if the wing has been a pediatric, gynecological, obstetrical or surgical wing, since none of these services would draw many lung cancer cases. Therefore, to make deductions as to whether even diagnosed lung cancer has or has not increased, using its percentage in total hospital admissions as a criterion is again a procedure which is likely to lead to erroneous conclusions.

If these bases of comparison, namely, total autopsies, total cancer autopsies and total hospital admissions are not trustworthy, what can we use to estimate how much diagnosed lung cancer has increased if at all? What shall we use as our standard of comparison? It is evident that since we are trying to deduce whether there has been any alteration in the ratio of diagnosed lung cancer cases in the population who are liable to develop lung cancer, the denominator of the fraction should be one which is kept as constant as possible, otherwise, variations in the ratio cannot be ascribed to changes in numerator, or lung cancer cases. Now, because sex plays a rôle, in some as yet undetermined manner, we should separate the lung cancer cases and the group used for a standard into males and females, and deal with the data for the two sexes separately.

Next we should keep the *age* factor as near constant as possible. This means that we should determine the ratio of

$$\frac{\text{lung cancer cases in the males in age groups 30-34}}{\text{standard quantity of males in age groups 30-34}}$$

Similar values for males between 35 and 39, 40 and 44, 45 and 49, etc., should be determined. Since the incidence of diagnosed lung cancer increases steadily with increasing age, at least up to 60, the age groups should be fairly small. Thus, to take groups from 40 to 60 for comparison gives too wide a range, for in one period most of the persons may have been just

over 40, whereas in the second period most of the persons may have been nearly 60

Having thus determined that our standard in the two periods under comparison shall be as near alike in age and sex distribution as possible, what shall the standard be? Hospital admissions, cancer autopsies, total autopsies? We have seen that many other factors influence these, and so make the denominators of our fractions vary

If hospital admissions be used as the standard of comparison, then it should not be all hospital admissions, but should be admissions separated into male and female groups, and further separated into age groups of five year periods. This will eliminate the most obvious and most easily corrected errors, but because hospital admissions are not representative samples of the community and because they are varying samples at different periods of time, such a comparison still does not give us unequivocal answers

If total autopsies be used as the standard of comparison, at least correction should be made for sex and age groups, as outlined above. Here the sample is even less representative than was the hospital sample, and the different diseases represented in the autopsy group are subject to more factors of selectivity than are the patients coming for admission to the wards

If *total proved cancer cases* are used as the standard, rather than total cancer autopsies, this would eliminate the criticism that biopsy and surgical specimens were being ignored in the later period, but even here the percentage of different cancers will vary in the two periods. If a large radium and roentgen-ray department has been established in the interim, skin, breast and uterine cancers will have been dealt with in excess proportion in the latter period, and we cannot be certain that our standard has remained unchanged. We shall be nearer to the truth, however, if we observe the above rules in determining the increase in lung cancer

There are two factors which seem to have been overlooked by many workers in all the methods used for determining lung cancer increase. (1) The space available in hospitals may not have increased in proportion to the population, therefore, the degree of selection in admission to the hospital in the first place largely influences the type of patient who ultimately comes to autopsy, apart from the selection acting on the patients after they get into the hospital. (2) The addition of one or two lung cancer cases to the number of this group alters the total of lung cancer cases tremendously, whereas the addition of the same number to the large number of cases being used as the standard alters that but little. For example, if we have 1000 general cancer autopsies in 1900, and 500 of these were in the gastrointestinal tract, the addition of five cases to this group would alter the percentage but little, changing it only from 50 to 50.5 per cent. But if we have five cases of lung cancer in this group to begin with, and add another five in a later period, we have doubled the percentage of lung cancer. Because of the very smallness in number of lung cancer cases in earlier periods, this particular type of cancer was in a strategic position to show a much higher rate of in-

crease with a little improvement in diagnosis than was almost any other cancer. Quite apart from any environmental factors causing its increase, its scarcity in the autopsy cases made it almost inevitable that unless all cases had previously been recognized, it was due to show a greater increase than were other forms of cancer.

As we are dealing with *diagnosed* lung cancer cases in either period of time, we should come nearer to a correct estimate of the increase in diagnosed cases if we were to use as our basis of comparison simply the population of a specified age and sex group in the period under discussion. Thus, if all hospitals in the United States or in a single state, or in Canada, or in England, were to send in a list of verified lung cancer cases for 1910, or for some year in which a census was taken, and if then the death rate from lung cancer per 100,000 for each five year age group of males and females were calculated and compared with similar figures for the year 1930 in the same country, we could see just how much *diagnosed* lung cancer cases were increasing, with some assurance that our standard of comparison was remaining stable. The separation into sex and age groups would compensate for any changes in the population, and we would not be comparing lung cancer cases with a standard that was fluctuating under as many variables as is the case with hospital admissions and autopsy records. Since we would be using verified lung cancer cases in each instance, our diagnosis would be as accurate as the fashion of diagnosis at the time would allow, and our standard would be much more stable than any other used. The numbers would be larger, and hence chance variations in different hospitals minimized. We still would not have found whether lung cancer had increased, but would find to what extent diagnosed lung cancer was increasing in men from the age of 50 to 55, or from 55 to 60. We should find the same facts for women of all age groups, and we would have only two possible variables with which to deal in our final analysis: (1) a possible percentage of the increase as due to actual increase, and (2) an unknown percentage of the increase due to more accurate diagnosis.

Even with these corrections we would probably find an increase in lung cancer, but I doubt if it would be nearly as large as most of the authors have stated. I should expect that lung cancer would show an increase for two reasons. (1) We cannot deny that the medical profession is much more alive to the possibility of there being such a condition than it was several decades ago, so that there is an undetermined increment of increase due to better diagnosis, even after age and sex have been compensated for. (2) People are not dying in middle-age today in as great numbers of tuberculosis, pneumonia, etc., as they did 30 years ago. Therefore, since they must die of something and since they are not being allowed to die of diseases that are amenable to modern treatment, they die of diseases over which as yet we have no control. Therefore, lung cancer, in common with other diseases for which there has been practically no improvement in therapy, shows an actual increase and will continue to increase until the reduction in deaths

from the other diseases ceases, or until improved surgery saves many more lung cancer patients from dying of their disease

Probably, however, there will not be found such an extraordinary increase of lung cancer as has been assumed to have occurred, an increase that has been held to be too great to be accounted for by these two factors of improved diagnosis and prevention of deaths due to other causes, always assuming that we have corrected for sex and age. The various attempts to find in the environment some explanation of this extraordinary increase in lung cancer will probably be futile, because we will probably find that there has been no such extraordinary increase. It is to be hoped that before many more environmental factors are advanced as causes of the increase in lung cancer, workers will more adequately control their studies to prove the great increase first, and hunt for the environmental factors afterward.

SUMMARY

Lung cancer has been stated to be increasing far faster than cancer in general has increased, because it has formed an increasingly larger percentage of total cancer autopsies. This paper points out some of the fallacies contained in such statements, and the suggestion is made that those who have large autopsy records of cancer in general and of lung cancer reexamine their material, and use the following methods to eliminate the most obvious sources of error in their material, methods which have been practically completely ignored in the study of this question.

1. Separate the lung cancer cases, as well as the group which is being used as the standard of comparison, into two groups according to the sex of the patients.

2. Separate these groups further into groups of not more than five year periods, thus comparing males of ages 30-34 who have lung cancer with males of 30-34 in the standard group. This will to a large extent eliminate criticisms that age and sex distribution are not the same in the periods under discussion.

3. If total cancer cases are still selected as the basis of comparison, use all histologically proved cancer cases on the records, whether the proof has been done on a biopsy, surgical or autopsy specimen.

4. The group of all the hospital patients, the group of all autopsied cases, and the group of autopsied cancer cases all probably deviate widely from the general population in the proportion of different diseases they contain because of the degree to which patients are selected for admission to hospitals, and to which patients who are in hospitals are selected for autopsy. This is due to a number of factors among them being (a) available space in hospital, (b) public health acts, and compensation acts which permit certain wage earners to be represented unduly in hospital and autopsy data, (c) desire of physicians to clear up obscure cases, or to let go without autopsy cases supposed to be clear, (d) awareness on the part of the profession of

the rarity or common occurrence of a disease, etc. In other words the hospital group, the autopsy group are not true samples of the population either in sex, age or disease distribution

5 The question we wish to determine is not whether lung cancer, meaning by that diagnosed lung cancer, is increasing in hospital cases, but is diagnosed lung cancer increasing in the population of the age and sex distribution which is capable of showing it? Therefore, the only way of determining this point is to study the incidence of diagnosed lung cancer in the population at large, and not in the small fragment of the population which comes to autopsy. Therefore, data from all hospitals within a state for two periods chosen so that the age and sex distribution of the population of the state is known, thus preferably in a census year, should be added together and analyzed. Cities are not large enough in their scope, since they draw obscure cases from surrounding rural areas in different proportions in various years. Each state, however, has usually centers that are apt to draw patients from within their own borders.

6 It will probably be found that diagnosed lung cancer is increasing both relatively and absolutely, but the increase will probably be much smaller by this method than by the ones adopted by most workers, in which age and sex distribution of the lung cancer cases and of the standard group were ignored. Lung cancer will be increasing because it is being diagnosed in more cases in which it exists than was formerly the case, and will be increasing no doubt because persons of lung cancer age are having fewer diseases to die of today than they had before, and hence must die in ever increasing numbers of the ones which remain.

7 The data which are used to support the idea that lung cancer has increased faster than other forms of cancer cannot be used to support that conclusion, since we do not know what proportion of lung cancer cases were unrecognized formerly and what proportion are unidentified today. We can merely state that *diagnosed* lung cancer is increasing at a rate which appears to be faster than that of other *diagnosed* cancers.

8 The search for environmental factors supposed to be the basis of the unduly great increase in lung cancer should await further proof that the increase in diagnosed cases has been as spectacular as it has been claimed to be.

INTERMITTENT CLAUDICATION. ITS TREATMENT WITH AN INSULIN-FREE, DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX) *

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THE term intermittent claudication was first used in 1831 by the French veterinarian Bouley¹ to describe a condition of limping in the horse, developing after a short period of exercise, recovering rapidly with rest, and found to be associated with an obliterative disease affecting the main artery of the leg. Subsequently several investigators, notably Brodie,² Charcot,³ and Erb,⁴ observed and described a similar condition in human patients, and as a result of their observations it was established that the usual anatomical defect associated with this condition is arterial occlusion and that the limping or lameness results most commonly from pain.

The pain which leads to intermittent claudication arises in the skeletal muscle of the extremity at a time when the muscle is working in a state of relative ischemia. Although the exact mechanism by means of which the pain arises is unknown, the investigations of Lewis, Pickering and Rothchild⁵ indicate that the pain results from stimulation of pain nerve endings in the tissue spaces of the muscles by a physiochemical stimulus developed in the muscle mass during exercise. The pain of intermittent claudication and that of angina pectoris present many similarities, and it is indeed probable that the mechanism of their production is similar if not identical.

It should be remembered that intermittent claudication is a symptom and not a disease. Therefore, any complete consideration of the condition from a diagnostic standpoint makes necessary recognition of the symptom itself as well as the malady which underlies and gives rise to it. Ordinarily recognition of intermittent claudication is not a difficult matter provided one is familiar with its characteristics. In the usual course of events the patient after walking for a block or two develops fatigue and pain in the arch of the foot, toes, ankle, calf, anterolateral aspect of the leg, knee or, less frequently, the back of the thigh. At times the discomfort assumes the form of a numbness occurring most commonly in the toes or the foot, either alone or more commonly in association with pain. Occasionally a patient is seen in whom the pain or fatigue levels off, as it were, at a point within the limit of his tolerance for these symptoms, and he is able to continue walking for long distances with only a moderate amount of discomfort. Continuation of walking, however, ordinarily results in limping, and soon he is forced, or deems it advisable, to stop and rest momentarily. Shortly after stopping the discomfort becomes less intense and usually disappears completely without

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one to five minutes, after which he resumes walking only to repeat the cycle of exercise, discomfort, limping and rest. At times more emphasis is placed by the patient upon the fatigue or numbness than upon the pain. However, in most cases close questioning will elicit the assertion that pain is the predominant factor which leads to the lameness. Although the pain may be variously described by the patient as cramp-like, burning, heavy, dull, aching, sharp, or in other ways perhaps, it has the essential characteristics of an onset only after a period of exercise, of constancy, of complete relief after a few minutes of rest, and of not being associated, except rarely, with an actual muscle cramp. Not infrequently unobservant patients will not define the characteristics of the pain or discomfort very clearly, and there will remain some doubt in the mind of the physician as to the correctness of the diagnosis of intermittent claudication. In such instances it is well to test the patient in the recumbent position by having him press the balls of the toes firmly and rhythmically against some resistant surface, or by having him walk under observation at a pace of 60 steps per minute, meanwhile observing the time required for the onset of pain and the cessation of exercise. If the tests are repeated, it will be found usually that the period over which a particular exercise can be continued is remarkably constant from time to time. Ordinarily either of these tests will give rise to marked fatigue, pain or numbness within a period of five minutes in patients who have any considerable degree of intermittent claudication.

The complaint of pain in the feet and legs is encountered very commonly in medical practice and, although the pain of intermittent claudication accounts for only a relatively small percentage of such complaints, it deserves consideration in all such patients owing to the seriousness of the lesion which always underlies it. Intermittent claudication is frequently overlooked, the pain being attributed to fallen arches, rheumatism, callouses, varicose veins, neuritis or any one of numerous other conditions. This is unfortunate, particularly in view of the ease with which the diagnosis can be established in most instances.

The presence of intermittent claudication always portends the presence of a serious underlying organic disease, usually of the vascular system, but occasionally of the blood itself. It is important, therefore, to establish the nature of the underlying malady which most commonly obliterates or appreciably narrows the main arteries of the extremity and causes severe impairment of its arterial circulation. The severity of the discomfort of an individual with this condition undoubtedly varies more or less directly with the degree to which arterial insufficiency of the muscle is present. However, the severity of the discomfort bears no such relationship to the extent of occlusion of the main arteries of the extremity. Rarely, intermittent claudication occurs in patients who have normal pulsation in the principal arteries of the extremity and, conversely, certain patients with extensive occlusion of the principal arteries of the extremities may have no intermittent claudication. In patients past 50 years of age, whether or not they have

diabetes, arteriosclerosis obliterans is the most frequent cause of intermittent claudication, whereas in patients under 45, thrombo-angitis obliterans is the most common offender. These two conditions cause intermittent claudication in by far the majority of instances. However, embolism, thrombosis of post-traumatic or infectious origin, aneurysm, arteriovenous fistula, and coarctation of the aorta, all producing severe impairment of the arterial circulation of the extremities, may lead to this condition. Occasionally a severe anemia may produce intermittent claudication in a patient apparently free from peripheral vascular disease⁶. Intermittent lameness may occur in the upper as well as in the lower extremity when pain results from exercise in the presence of impairment of the arterial blood flow to the muscles of this region. Occasionally it occurs in the upper extremity in the presence of an old arterial thrombosis secondary to a cervical rib or a scalenus anticus syndrome.

The treatment of intermittent claudication is difficult and on the whole unsatisfactory. Inasmuch as it arises most commonly as a result of arterial circulatory impairment, ideal treatment should aim at eradication of the condition giving rise to the circulatory disturbance. Although in an occasional case of arteriovenous fistula or anemia producing intermittent claudication the underlying defect is amenable to eradication by proper therapy, such cases are the exception rather than the rule. The majority of the cases, by far, arise as a result of obliterative arterial disease, and eradication of the underlying condition is impossible. The treatment, therefore, is aimed at improvement of the underlying circulatory defect rather than at its elimination. Wright⁷ has recently presented an excellent discussion of the various methods of treating arterial circulatory insufficiency and its complications and, excepting pancreatic tissue extract, no attempt will be made here to comment on this rather complex subject. It should be pointed out, however, that aside from the use of tissue extracts the methods most widely used at the present time for the treatment of arterial occlusion are not very successful in the treatment of intermittent claudication.

Interest in the treatment of intermittent claudication with tissue extracts began in 1926 with the work of Frey and Kraut, who prepared a pancreatic extract, Kalledrein (Padutin), which was reported to inhibit the pain producing intermittent claudication. Subsequently, several investigators^{8, 9, 10} reported favorably on the use of pancreatic extracts in the treatment of this condition, and recently favorable reports concerning the use of an insulin-free, deproteinated pancreatic extract (Depropanex) in the treatment of intermittent claudication associated with arteriosclerosis obliterans have appeared^{11, 12}.

Depropanex* is a colorless saline solution of a chemically purified protein-free, nitrogenous fraction obtained from an acid-alcohol extract of beef pancreas. Physiological tests show that it is free from insulin, histamine and acetylcholine. It contains approximately 2.5 per cent solids, including

* Supplied us by courtesy of Sharp & Dohme

0.5 per cent non-protein nitrogen, 0.9 per cent sodium chloride and 0.25 per cent phenol, as a preservative. It is adjusted to a pH of 6.5 to 6.88.

We have had occasion recently to observe 15 patients with intermittent claudication who were treated with Depropanex. The present report summarizes our results.

METHOD OF STUDY

In order to measure accurately the claudication time, we utilized an apparatus similar to that described by Fisher, Duryee and Wright,¹² by means of which the work performed per unit of time could be controlled. It consisted of a vertical stand to which was attached a foot pedal. A weight of 13.6 pounds was connected with the pedal by means of a rope and pulley in such a manner that depression of the pedal resulted in an elevation of the weight through a distance of approximately seven inches. The weight was elevated and lowered by the patient as he sat in a chair in front of the apparatus and pressed the pedal with his foot at a rate of 60 times per minute. The rate at which the weight was elevated and lowered was regulated by means of a metronome. We instructed each patient to inform us when fatigue and pain began in each muscle group, and to continue the exercise until the pain became so severe as to preclude any continuance. The times of onset of fatigue and pain and of cessation of exercise were determined by means of a stop watch. The time elapsed between the points of onset and cessation of the exercise was considered to be the "claudication time." Case 2, who had had both lower extremities amputated previously and who complained of pain with exercise in the right upper extremity, was tested by having him compress a rubber bulb with the hand at a rate of 60 times per minute.

A patient in whom the claudication time was to be determined was allowed to rest for a period of 20 minutes prior to the start of exercise. Two tests were performed on successive days, and following the second test the first injection of Depropanex was given into the deltoid muscle. Following the first injection a rest period of 30 minutes was allowed and then a third test was performed. The injections were given every other day in all cases with one exception, Case 1, who received daily injections. During the course of the injections exercise tests were performed at two to six day intervals, and 48 hours after the last injection a final exercise test was performed.

A total of 15 cases were treated, nine of whom had thrombo-angitis obliterans and six arteriosclerosis obliterans. All of the patients were ambulant, and none had any areas of ulceration or gangrene present at the time of the investigation. None of the patients, as far as we could determine, had been treated previously with tissue extract.

The studies of the effect of Depropanex on the blood pressure, pulse and skin temperature were performed in a room which was controlled to give a constant temperature of 71° F plus or minus 1°. The pulse rate was de-

terminated with the aid of a stop watch, the blood pressure taken with a standard type mercury monometer, and the skin temperature measured by means of a Taylor Dermatherm

Prior to making observations relative to the effect of Depropanex on the blood pressure, pulse and skin temperature, we allowed the patient to recline on a bed in the constant temperature room for a period of sufficient length to allow stabilization of the blood pressure, pulse and skin temperature, usually one-half to three-quarters of an hour. He was covered with a sheet, the hands and feet remaining exposed at room temperature. Determinations of the pulse rate, blood pressure and skin temperature of the volar surfaces of the distal phalanges of one toe and one finger were then begun and continued at five-minute intervals for 30 minutes in order to establish a reliable base line. An intramuscular injection of Depropanex was then given, and determinations of the pulse, blood pressure and skin temperature were continued at five-minute intervals. A similar procedure was followed in those instances in which only the blood pressure and pulse rate were observed.

Results The effect of Depropanex on the claudication time of 15 patients is shown in table 1. Of the nine patients with thrombo-angitis ob-

TABLE I
Effect of Depropanex on Claudication Time of Patients with Occlusive Arterial Disease

Case No	Diagnosis	Age	No Injections	Amount of Each Injection c c	Average C T Before Dpx	C T 30 Min After First Injection	C T 48-72 Hrs After First Injection	Final C T	Region Pain Most Severe
1*	TAO	45	10	3	1' 15"	1' 32"	1' 10"	3' 10"	Calf
2	TAO	30	10	3	2' 25"	3' 12"	2' 15"	>10' 0"	Calf
3	TAO	50	5	3	1' 15"	2' 27"	2' 13"	8' 20"	Arch
4	TAO	40	10	3	2' 10"	3' 15"	6' 0"	>10' 0"	Calf
5	TAO	46	10	3	3' 40"	5' 20"	4' 45"	7' 50"	Hand
6	TAO	34	10	3	3' 0"	3' 40"	6' 15"	>10' 0"	Arch
7	TAO	37	10	3	2' 0"	2' 12"	2' 42"	>10' 0"	Calf
8	TAO	38	10	3	2' 12"	2' 16"	2' 28"	2' 48"	Calf
9	TAO	48	4	5	0' 53"	0' 45"		0' 40"	Calf
10	ASO	70	10	3	1' 45"	2' 15"	2' 57"	2' 25"	Calf
11	ASO	59	10	3	1' 30"	1' 24"	1' 24"	1' 32"	Calf
12	ASO	51	6	3	1' 32"	1' 32"	2' 45"	1' 48"	Thigh
13	ASO	60	10	3	1' 0"	1' 5"	1' 7"	1' 8"	Calf
14	ASO	52	10	3	1' 55"	1' 27"	2' 20"	2' 27"	Thigh
15	ASO	51	10	3	2' 0"	2' 0"	2' 2"	1' 44"	Calf

* Received injections daily
C T = Claudication time
DP\ = Depropanex

TAO = Thrombo-angitis Obliterans
ASO = Arteriosclerosis Obliterans

literations studied, seven were improved and two were unimproved as indicated by the claudication tests performed before and following the treatment. Three patients could exercise greater than two times, and four patients greater than four times as long following the treatment as was the case beforehand. Of the six cases of arteriosclerosis obliterans treated none showed an increase in claudication time of more than 40 seconds at the end of the period of treatment, and it must be concluded, therefore, that there was

no appreciable improvement in this group of patients as a result of the treatment

The Effect on Pulse, Blood Pressure and Skin Temperature In four patients observations of the pulse, blood pressure and skin temperature were made for a period of one hour following intramuscular injection of 3 c c of Depropanex. In an additional five patients observations were made in 15 instances of the pulse rate and blood pressure only for a period of 30 minutes following the intramuscular injection of 3 c c of Depropanex. The results of these observations are presented in table 2. In the 19 instances in which the blood pressure was studied for 30 minutes following the injection of Depropanex, the greatest increase noted was 30 mm of mercury in the systolic pressure and 14 mm of mercury in the diastolic pressure. The greatest decrease in systolic pressure was 16 mm of mercury and in the diastolic pressure 10 mm of mercury. In 18 of the 19 instances the changes in blood pressure were less than 20 mm of mercury, and in 15 of the 19 instances the changes were less than 15 mm of mercury within 30 minutes after the injection. The changes were consistently neither pressor nor depressor in character. In the four instances in which the blood pressure was followed for an hour the greatest increase in systolic pressure noted during the second 30-minute period was 30 mm of mercury, and the greatest decrease in systolic pressure during the second 30-minute period was 14 mm of mercury, and the greatest decrease in diastolic pressure was 5 mm of mercury. Here again the blood pressure changes were consistently neither pressor nor depressor in character, although the tendency was more in the direction of a pressor effect.

The changes noted in pulse rate and the temperature of the skin of the digits following 3 c c of Depropanex intramuscularly were not remarkable.

Four of the subjects developed a slight headache 20 to 30 minutes following injection of the Depropanex, the headache lasting from five to 10 minutes. None of the patients complained of pain or tenderness at the site of injection, either at the time of injection or afterward. No other untoward symptoms were reported subsequent to injection.

COMMENT

Our studies indicate that certain patients with intermittent claudication are enabled to perform more exercise as a result of injection of an insulin-free, deproteinized pancreatic extract. This improvement occurs as a result of a lessening of the pain and fatigue which leads to this condition. It is doubtful if the underlying disease state is appreciably influenced by this treatment. Our results with Depropanex in the treatment of patients with intermittent claudication due to thrombo-angitis obliterans have been fairly good. In patients with intermittent claudication due to arteriosclerosis obliterans, on the contrary, our results have been unsatisfactory. However, the number of cases with arteriosclerosis treated by us has been small and it is possible that

TABLE II
Effect of Depropanex on Blood Pressure, Pulse Rate and Skin Temperature

Test No	CONTROL PERIOD BEFORE DEPROPANEX										AFTER I M INJECTION 3 cc DEPROPANEX										Case* No					
	B P					Skin temp ° C					Maximum change 30 min					Maximum change 30-60 min										
S	D	Pulse	Finger	Toe	S	D	Pulse	F	T	S	D	Pulse	F	T	S	D	Pulse	F	I							
1	132	98	76	26.1	23.0								-16	-8 +12	+4	-8	+13	-9	+14	+18	-6	+24	+16 -9	-14	1	
2	110	75	68	26.3	24.5								+2 -2	+3	+4	-8	+2 -7	-7	-2	-5	-8			+5	-4	2
3	150	96	68	31.0	23.1								+30	+14	-4		-4 +5	-12	-12	+14 -1	-13	+17	+6	-8 +4	3	
4**	85	60	60	30.5	23.5								+12	+14	+12	-12	-4 +2	-7	+23	+20	+12	-4	-39	-8		
5	128	84	80										+10	+8	+8										4	
6	126	80	78										-10 +2	+4 +4	+2											4
7	120	80	80										+2	+10	+4											4
8	118	70	88										-2	+6	-8											5
9	130	80	80										+4 -4	-2	0											5
10	132	80	74										-14	-6	+4											5
11	118	78	80										0	0	0											6
12	108	76	72										+10	+8	+8											6
13	100	78	72										-4	-10 +2	+8											6
14	108	72	80										+8 -10	+12 -8	+8											6
15	110	78	81										-16	-10 +4	+4											6
16	112	78	88										-12	-10	0											6
17	116	78	88										-16	-4	-8											6
18	118	76	80										+14	+12	-8											10
19	100	65	92										+10 -3	+5 -2	0											9

* Case numbers here correspond to those in table I

** This patient was convalescing from an attack of rheumatic fever and had no peripheral vascular disease

our patients constituted an unusually difficult group to treat. In contrast to our experience, Fisher, Duryee and Wright¹¹ have reported favorably on the treatment of intermittent claudication in arteriosclerotics, and their study included a much larger number of patients. Therefore, the general conclusion seems warranted that in patients with intermittent claudication due to either thrombo-angitis obliterans or arteriosclerosis obliterans some of the patients are improved, whereas some are not. In the light of our experience, there is no method of predicting which patients will be improved excepting that of therapeutic trial. However, we have gained the general impression that a patient with profound ischemia is less likely to obtain improvement than one whose arterial circulation is only slightly or moderately impaired.

The problems of optimal dosage, mechanism and duration of action, and the utilization of other fractions as applied to pancreatic extracts deserve further consideration and clarification.

SUMMARY

A discussion of the diagnosis of intermittent claudication and a study of its treatment with an insulin-free, deproteinized pancreatic extract (Depropanex) is presented. The study indicates that this substance is of value in the treatment of some patients with intermittent claudication due to thrombo-angitis obliterans. Following the intramuscular injection of 3 c.c. of this substance, no remarkable changes in blood pressure, pulse rate and digital skin temperature were noted.

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CASE REPORTS

PROLONGED ADMINISTRATION OF SULFAPYRIDINE IN SUBACUTE BACTERIAL ENDOCARDITIS, REPORT OF CASE FOLLOWING ADMINISTRATION OF 621 GRAMS*

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THE literature is replete with reports of the various toxic effects of sulfapyridine. Of principal importance are the effects on the blood, urinary tract, and liver. The occurrence of agranulocytosis was originally reported by Johnston,¹ later followed by Coxon and Forbes,² Barnett et al,³ Shullenberger,⁴ and others. Acute hemolytic anemia was noted by Long and associates⁵ in 0.6 per cent of 297 cases treated with sulfapyridine. The deposition of acetylsulfapyridine calculi in the urinary tract of experimental animals was first reported by Antopol and Robinson,⁶ and by Gross, Cooper and Lewis,⁷ and shortly afterward Southworth and Cooke⁸ described the occurrence of hematuria, abdominal pain (of renal origin) and nitrogen retention in man. Numerous reports have appeared since. Toxic hepatitis has been reported,^{9, 10} but is extremely rare. Recently Rake, van Dyke, and Corwin¹¹ have noted pathologic changes in the livers of mice following sulfapyridine administration, but observed none in the rat and monkey. Purpura and anuria have been reported. The other less serious manifestations of sulfapyridine are well known and warrant no comment. In view of the numerous toxic effects of the drug, its prolonged administration might be expected to lead to serious reactions. However, following is a case in which, with the exception of occasional nausea and vomiting during the first month, no detrimental effects were observed either clinically or at autopsy.

CASE REPORT

M S, a white female, aged 47, housemaid, was admitted to Welfare Hospital July 14, 1939, with a history dating back to 1933 when she suffered a fracture of the right ankle, for which she was hospitalized. A routine examination revealed she had rheumatic heart disease with auricular fibrillation. Two months later she was transferred to a second hospital where she remained for six years. During this period, owing to the development of ankylosis of the right ankle, her physical activities were limited. In 1939 she was transferred to Welfare Hospital. Past history revealed chorea at the age of 15 persisting for one year.

Physical examination. Oral hygiene was poor and moderate dental caries was present. The maximum cardiac impulse was in the fifth left interspace in the mid-clavicular line. A thrill was palpable at the third and fourth left interspaces. A presystolic murmur was audible at the apex and mitral area, followed by a sharp, loud

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first sound. A systolic murmur was present at the aortic area. Rhythm was grossly irregular. The precordial rate was 80, and there was no pulse deficit. The right ankle revealed a marked inversion ankylosis. The rest of the examination was essentially negative.

Laboratory examination. Urine was normal. Blood count revealed 82 per cent hemoglobin, 4,200,000 red blood cells, 10,600 white blood cells, with 62 per cent polymorphonuclears, 37 per cent lymphocytes, and 1 per cent mononuclears. Blood chemistry was normal. Blood Wassermann and Kline reactions were negative. An electrocardiogram revealed auricular fibrillation and digitalis effects.

Course in the hospital. The patient was gradually allowed out of bed, manifesting no signs of cardiac decompensation. On September 14, 1939 (two months after admission), her temperature rose to 101.6° F and six days later returned to normal spontaneously. One week later her temperature rose to 102° F, and a blood count revealed 13,200 white blood cells with 82 per cent polymorphonuclears and 18 per cent lymphocytes. Urine disclosed a trace of albumin. Because of the appearance of pulmonary signs sulfapyridine administration was begun, causing a return to normal temperature within 24 hours. Sulfapyridine was discontinued at the end of five days, following the administration of 22 grams. The temperature immediately became elevated, but was followed by a spontaneous remission one week later. On October 19, 1939, her temperature again rose and remained between 100° F and 101° F for 11 days, during which period two blood cultures were positive for *Streptococcus viridans*, 7 colonies and 14 colonies per c c. On the eleventh day (October 30) sulfapyridine therapy was begun, and was maintained until November 5, the patient receiving 23 grams. On November 6 the temperature again became elevated and on November 8 sulfapyridine therapy was again begun. Three days later the temperature returned to normal, and except for an occasional slight rise remained normal for two months, the patient receiving 168 grams during this period. Her temperature remained normal for three weeks after discontinuance of sulfapyridine, but on January 24, 1940 the temperature rose to 100.8° F, reaching 102° F two days later. On January 27 sulfapyridine administration was once more begun and maintained until her death five months later, the dosage for this period being 408 grams. On May 15, 1940, the patient suddenly developed cerebral embolism with right hemiplegia, and died May 18, 1940.

During the course of sulfapyridine therapy blood sulfapyridine studies revealed the concentration of free sulfapyridine usually between 6 and 10 mg per 100 c c but varying between 3.2 mg and 10.7 mg per 100 c c. Total sulfapyridine ranged between 7 and 11 mg per 100 c c reaching a low of 3.5 mg and a high of 13.2 mg per 100 c c. The sulfapyridine dosage was usually maintained between 3 and 5 grams daily orally (with sodium bicarbonate) but varied from 1 gram to 7 grams. Repeated urinalyses were normal except for traces of albumin, and the inconstant presence of red blood cells varying in number from 1 to 20 per high power field (which was thought to be due to the syndrome of subacute bacterial endocarditis). At no time were sulfapyridine crystals present despite repeated careful search. Blood counts revealed a fairly constant hemoglobin content of 80 per cent but exhibited occasional variations between 70 per cent and 91 per cent. Red blood cells averaged 4,300,000 with a low immediately preceding death of 3,326,000, and a high of 4,680,000. White blood cells ranged between 7,900 and 20,400, polymorphonuclears were 62 per cent to 92 per cent, lymphocytes 8 per cent to 37 per cent. Determinations of blood non-protein nitrogen, urea nitrogen, creatinine, uric acid, sugar, sodium chloride, cholesterol, and cholesterol esters, were always normal. Icteric index never exceeded 5.8 units. Spectroscopic examination of the blood revealed no sulfhemoglobin or methemoglobin. A red blood cell fragility test revealed hemolysis beginning at 65 per cent and complete at 25 per cent. Red blood cell volume per cent, number per cent, and volume index were normal. Blood sedimentation rates were constantly between 29 and 31 mm in one hour.

(Cutler method) There were seven positive and 14 negative blood cultures for *Streptococcus viridans*. The roots of five of the seven extracted teeth yielded positive cultures for *Streptococcus viridans*, and were considered the primary foci of the blood stream infection. A galactose tolerance test was normal. A Mosenthal test and Addis count were normal.

NECROPSY

Gross Description Brain An area of softening involving the left caudate nucleus, lenticular nucleus, and internal capsule was present. The center of this area was necrotic and vacuolated, and the periphery was hemorrhagic. A large well organized thrombus completely occluded the left middle cerebral artery. Lungs Bilateral congestion and edema were present. The right lung showed a moderate degree of atelectasis. Heart Weight 440 grams. Old fibrous bandlike adhesions were present between the left ventricle and the pericardial sac. The right auricle was slightly dilated. The tricuspid valve measured 12 cm, and was moderately thickened, the chordae tendineae were thickened and shortened. The pulmonary valve showed no abnormalities. The left auricle was dilated and the auricular endocardium was thickened. A large thrombus filled the whole left auricular appendage and was adherent to its wall. The mitral valve was stenotic and measured 7.5 cm. Shortening and thickening of the chordae tendineae were present. Numerous small and large vegetations were present on the mitral valve, the smallest the size of a pinhead, the largest 1.25 cm in diameter. These were soft, friable and red. The aortic valve was 7 cm in diameter, thickened and calcified. Both ventricles were hypertrophied, the left also slightly dilated. Gastrointestinal tract normal. Liver Weight 1250 grams. The surface was smooth, the edge sharp, and the color dark bluish-red. Cut section disclosed a homogeneous dark reddish soft liver tissue. Gall-bladder revealed cholesterosis. Spleen A fairly old infarct 1¾ cm in diameter was present. Pancreas normal. Kidneys (See figures 1 and 2) The surface of the kidneys showed a few deep scars similar to those found in arteriosclerotic kidneys. There were no petechiae. The left kidney showed fetal lobulations. An average amount of cortex and medulla was present in both kidneys. The vessels of the cortex and medulla were prominent. The calyces, pelves and ureters contained no calculi, amorphous sediment or crystals. A congenital double pelvis and ureter were present on the left side. Ureters There was no obstruction. The left ureter was double. Bladder normal. No calculi were present. Genital Tract The tubes and ovaries were senile in type. Adrenals Both were of average size and shape. Marked postmortem degeneration was present. Extremities The right ankle revealed complete ankylosis with inversion.

Microscopic Description Heart The mitral, tricuspid and aortic valves were markedly thickened by fibrous and hyalinized tissue, vascularity was increased. In the mitral valve near these vessels groups of large pale cells with vesiculated nuclei were seen. An occasional group of cells surrounded by pink-staining necrotic material was noted. On the surface of the valve an acellular exudate was adherent in areas. Near the point of adhesion massive collections of polymorphonuclears, lymphocytes and plasma cells were visible. In other areas of the valve large groups of lymphocytes were present. Occasional small masses of bacteria were present on or near the valve surface. The tricuspid valve disclosed old Aschoff bodies and streaks of lymphocytes. An area of calcification and cells resembling old Aschoff bodies were observed in the aortic valve. Many myocardial cells were hypertrophied, others showed pyknosis of their nuclei with granular degeneration of the cytoplasm. Marked obliterative thickening of the coronary vessels was present. In many of the perivascular spaces Aschoff bodies were observed. Small patches of myocardial fibrosis infiltrated with lymphocytes were present. Liver No abnormalities were seen. Spleen Moderate congestion was present. Areas of varying size composed of

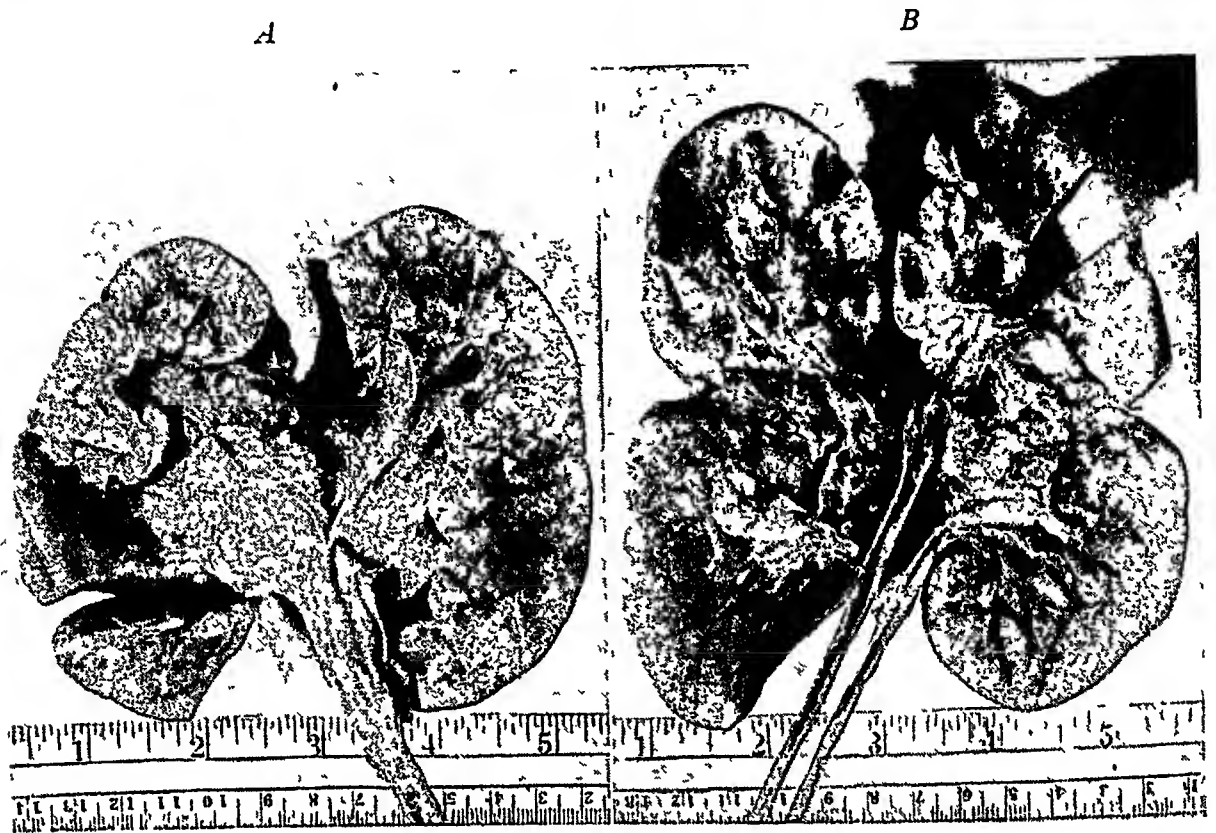


FIG 1 Right kidney and ureter (A) and left kidney and ureter (B) showing no calculi or pathologic changes attributable to sulfapyridine. Note congenital double pelvis and ureter of left kidney.

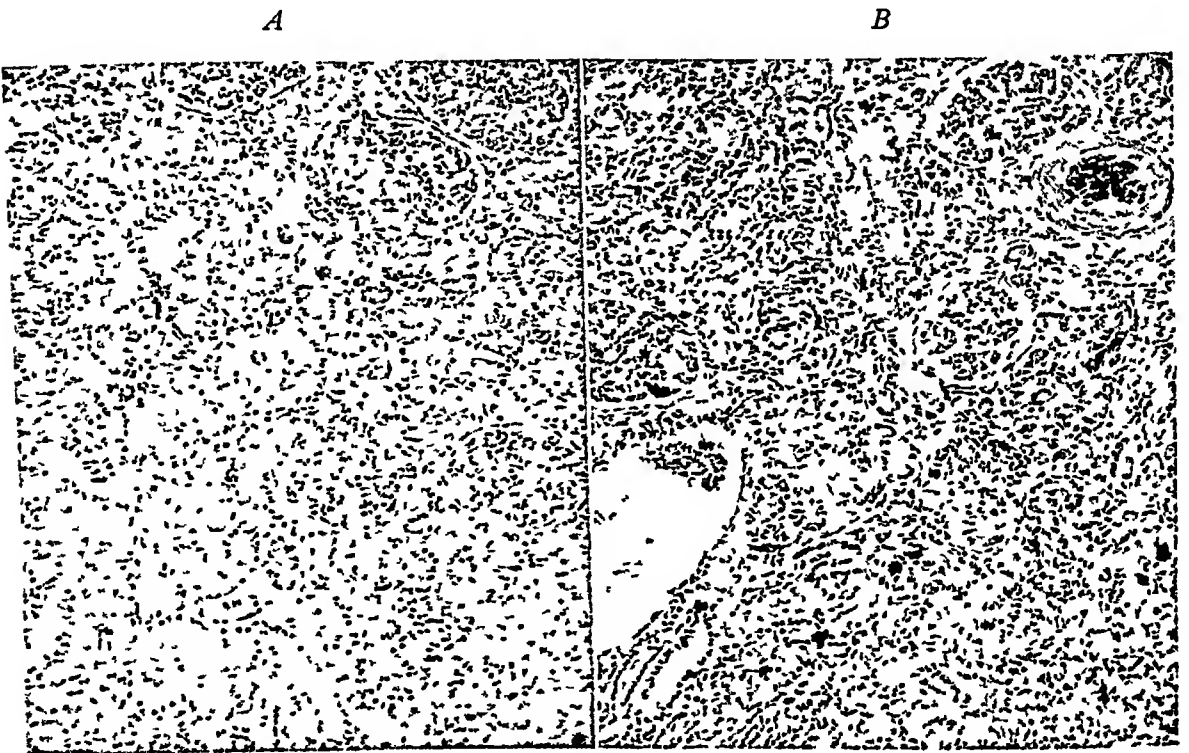


FIG 2 Microscopic section of each kidney (A and B) showing no concretions or other pathologic effects of sulfapyridine.

necrotic acellular material were seen. Some of these areas were relatively fresh, and red cells and lymphocytes were still visible. The vessels were markedly thickened. Kidneys: Slight congestion was present. Fibrous areas of varying sizes were seen. Enmeshed in the fibrous tissue were numerous lymphocytes and fibroblasts. The interlobular arteries were moderately thickened. A moderate number of hyalinized glomeruli was noted. No crystals, amorphous sediment, or calculi were seen in the glomeruli or tubules.



FIG 3 View of heart showing left auricle and auricular appendage, mitral valve, and left ventricle. Note thrombus in auricular appendage, and large friable vegetations on mitral valve.

COMMENT

Mild nausea and vomiting occurred occasionally during the first month but never necessitated discontinuing the drug. The presence of red blood cells in the urine warrants mention. Their inconstant occurrence, limited number, the absence of gross hematuria, absence of sulfapyridine crystals in the urine, and the frequency with which this finding is noted with subacute bacterial endocarditis caused us to assume that it was probably not a manifestation of sulfapyridine toxicity. Sodium bicarbonate was administered in conjunction with the sulfapyridine, but the literature contains no convincing evidence to indicate that it prevents the deposition of acetylsulfapyridine calculi.

The administration of sulfapyridine in excess of 500 grams has been reported by Plummer and McLellan,^{1,2} autopsy disclosing calculus formation and petechial hemorrhages in the renal pelvis. Long¹³ and Plummer¹⁴ have informed us of several cases in which the dosage has exceeded 500 grams and in which no toxic effects have occurred. However, no data are available regarding possible tissue damage.

It would appear from the observations of others,^{13,14} as well as from our case, that sulfapyridine administration may, in certain individuals, be maintained for unusually long periods without toxic effect. It is possible, as Long¹³ suggests, that the drug may be tolerated indefinitely if toxic reactions do not appear within the first 45 days of its administration.

SUMMARY

We have presented a case in which 621 grams of sulfapyridine were administered over a period of eight months. No untoward effects were observed except for the occurrence of mild nausea and vomiting during the first month. At necropsy the organs revealed no characteristic changes attributable to sulfapyridine. The literature contains no previously reported case of the administration of so large a dosage of sulfapyridine with absence of clinical and postmortem evidence of toxicity. The case is of interest in view of the frequency with which toxic reactions appear when the usual therapeutic dosages are employed.

We wish to express our appreciation to Dr J Rosenthal and the Pathology Department for their excellent cooperation.

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OBSERVATIONS ON A CASE OF INTERMITTENT POSTURAL HYPOTENSION*

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POSTURAL hypotension is a syndrome characterized by the occurrence of a fall of arterial pressure when an upright posture is assumed. In that form of the malady which was first described by Bradbury and Eggleston,¹ the fall of arterial pressure is accompanied by relatively little or no increase in heart rate. The prevalent opinion is that the fall of pressure in cases of this type is owing to a defect of the reflex vasoconstrictor mechanism which adapts the circulation to changes in posture^{2, 3, 4}. It has also been suggested, however, that the underlying fault consists of an inadequate return of venous blood to the heart⁵.

An unique approach to the study of postural hypotension was afforded by a case in which the syndrome could be completely abolished by a number of different procedures. This case is also of interest because the hypotensive reaction was intermittent. Remissions in the occurrence of syncope and variations in the levels to which the blood pressure rises and falls are common, but there appears to be no previous report in the literature of repeated complete disappearance and recurrence of the entire syndrome over a period of many years.

CASE REPORT

T S, a colored male, now 55 years old and a stevedore by occupation sustained a fracture of the right tibia in 1931. Thereafter he noted occasional faintness on standing but never lost consciousness and was promptly relieved by lying down. The fracture failed to unite and in 1933 the insertion of a bone graft was attempted at the Graduate Hospital. Following anesthetization by avertin and ether, the patient suddenly became pulseless and the blood pressure could not be recorded. Prompt recovery was obtained by the injection of adrenalin, but the operation was postponed pending further study.

The report of a cardiac consultation in February 1934 stated that the blood pressure was 230 mm Hg systolic and 154 mm diastolic, but the heart presented nothing abnormal on physical, electrocardiographic or fluoroscopic examination and the patient was apparently a good surgical risk. One month later the operation was performed without complication under spinal anesthesia. The patient was followed in the Medical Clinic and in November 1935 was transferred to the Heart Clinic. He stated that he had recently begun to have recurrent substernal pain, unrelated to physical exertion, and had noticed increasingly frequent dyspnea and palpitation on standing or walking. He had been unable to work since his accident in 1931.

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Pertinent features of the past medical history were as follows. The patient had gonorrhea at 19. A prostatic punch operation for urinary incontinence had been performed at 49. In the same year syphilis had been discovered but a course of antisyphilitic treatment had been discontinued before its completion.

Physical examination revealed a well nourished and intelligent man of average build who appeared about 10 years younger than his stated age. The skin was dry. The lymph nodes were not enlarged. The palpable arteries were not abnormally sclerotic. The lungs, heart and abdomen showed no abnormalities. There was no edema of the extremities. On neurologic examination, the only abnormal signs noted were fixed pupils, absence of knee jerks, and trophic skin changes on both lower limbs. Blood count and urinalysis were essentially normal. Kahn and Eagle tests were positive. The basal metabolic rate was minus 10 per cent. A diagnosis of hypertensive cardiovascular disease and cerebrospinal syphilis was made.

From November 1935, until April 1938, the patient made 25 visits to the Heart Clinic, and on 20 of these the blood pressure, seated, was above 150 mm Hg systolic and 100 diastolic and averaged 200 mm systolic and 130 diastolic. The pulse rate averaged 80 per minute. On four visits, the blood pressure was lower than 150 mm Hg systolic and 100 diastolic, on one occasion being 120 mm systolic and 80 diastolic.

On April 1, 1938, the blood pressure, seated, was found to be 98 mm Hg systolic and 60 mm diastolic, and recent myocardial infarction was suspected. An electrocardiogram, however, was normal, and the patient stated that he had been feeling somewhat faint but certainly no worse than at frequent intervals during the past seven years. Blood pressure was then measured in the recumbent posture and found to be 135 mm Hg systolic and 75 mm diastolic. Upon standing it became unmeasurable, and the patient complained of severe dizziness. The condition was thereupon recognized as postural hypotension of intermittent occurrence.

METHODS

The studies to be reported were carried out in the course of afternoon visits of about three hours' duration. The patient had usually eaten little or no lunch. Following a preliminary rest period, repeated determinations of pulse rate and blood pressure (the latter measured by the auscultatory method from the left arm) were made in relation to the procedures which will be described. Since 1939, the episodes of orthostatic hypotension have apparently ceased to occur. For this reason, and because the hypotensive reaction was inconstant, some of the observations which follow could not be repeated and certain contemplated studies could not be carried out.

OBSERVATIONS

The Association of Hypertension with Orthostatic Hypotension. Some degree of hypertension is noted in the records of occasional cases of orthostatic hypotension^{1, 6, 7, 8, 9}. In these cases, however, the hypertension was observed only in the recumbent posture or was inconstant, the blood pressure tending to fluctuate within rather wide limits. In the present case the blood pressure reached and persistently maintained such high levels as 200 to 230 mm Hg systolic and 140 to 150 mm Hg diastolic. Only one report of a case comparable in this respect could be found in the literature.⁷ As will later be described, the high pressures occurred most frequently (but not always) at times when the hypotensive reaction was absent or only slightly manifest. When the hypotensive reaction was marked, the recumbent pressure was usually lower, 130 to 180 mm Hg systolic and 90 to 125 mm Hg diastolic.

Effect of Change in Posture Change from a recumbent to a standing posture produced, at different times, each of the following effects on blood pressure (1) A fall, averaging 50 to 100 mm Hg systolic and 15 to 55 mm Hg diastolic, followed by persisting hypotension (figure 1, a) (2) A fall, similar to the above, but followed by a gradual rise over a period of 10 to 30 minutes, to a point approximately the same as, or exceeding, the recumbent level (figure 1, b) (3) A fall, similar to the above, but followed by a prompt rise over a period of three minutes or less, to a point approximately the same as, or exceeding, the recumbent level (figure 1, c) (4) Either no change or a slight rise (figure 1, d)

On those occasions when the hypotensive reaction was manifest, standing up usually produced a fall of pressure with persistent hypotension. After two or three hours, however, a more or less rapid rise of blood pressure followed the initial fall. On those occasions when the hypotensive reaction was not immediately manifest, little or no fall of blood pressure on standing was observed during the subsequent three hour period.

The heart rate always increased slightly on change from a recumbent to a standing posture but, as is characteristic of "classical" orthostatic hypotension, it never increased to an extent commensurate with the fall of blood pressure. The recumbent heart rate averaged 70 per minute and increased on standing to an average of 76 to 92. The increase was greatest when the fall of blood pressure was most pronounced.

Sweating, as judged by the presence of perspiration on the face or body, was often present when the blood pressure was high but was absent, even on very hot and humid days, whenever the blood pressure was low. The only exception, which will later be described, was when sweating accompanied a fall of blood pressure caused by immersion of the hand in painfully cold water.

Faintness occurred when the blood pressure reached levels which were scarcely measurable, such as 65 mm Hg systolic and 60 mm diastolic, and the patient was then forced to support himself against a table. Faintness never progressed, however, to the point of complete loss of consciousness. Attention is drawn to the fact that no subjective sensations whatever accompanied the abrupt changes in blood pressure which occurred between such extreme levels as 220 mm Hg systolic and 130 mm diastolic and 90 mm systolic and 70 mm diastolic.

Change in position of the head, in the standing or recumbent posture, without change in position of the body, had no significant effect on blood pressure or pulse rate.

Effect of Arresting the Blood Flow to Active Muscles Active movements of an arm or leg to which the circulation has been arrested by an inflated manometer cuff is followed by a rise of blood pressure in normal persons.¹⁰ This effect has been attributed to a vasoconstrictor reflex, the receptor endings of which are situated in the muscles of the limbs (and probably also in other parts of the body) and are presumably stimulated by the local accumulation of tissue metabolites. In the present case, the magnitude of the rise in blood pressure produced in this manner is without precedent in the literature. The following example is typical of the results invariably obtained. In the standing posture, blood pressure being continuously about 85 mm Hg systolic and 60 mm diastolic, circulation in the leg muscles (which were active in supporting the

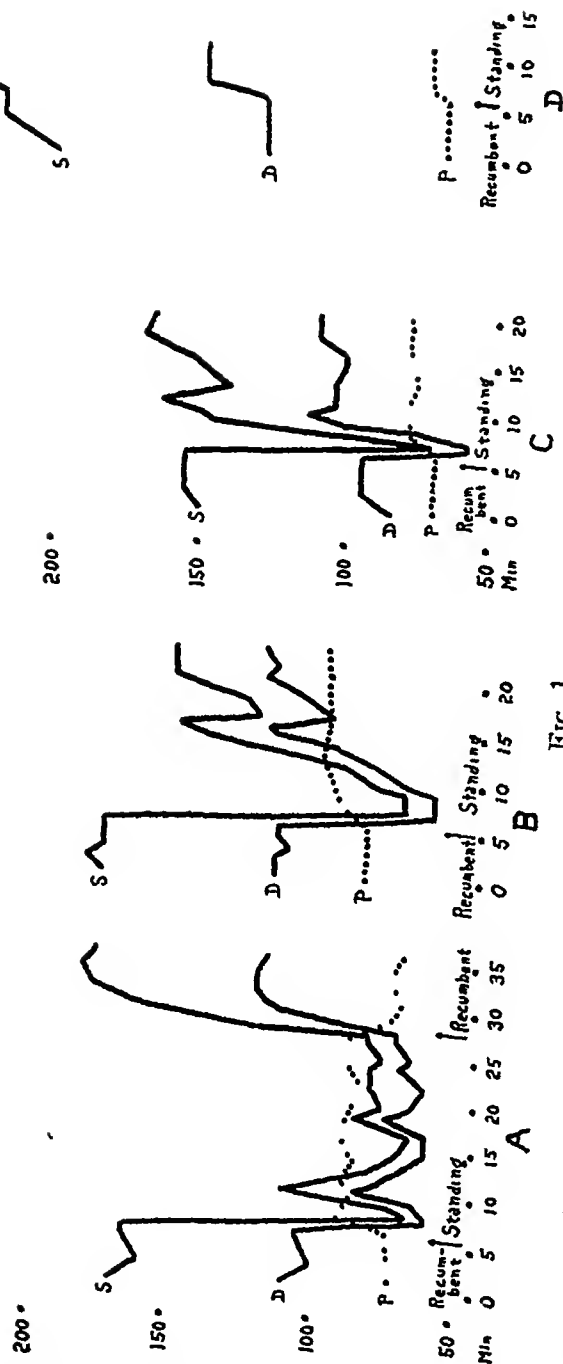


FIG 1

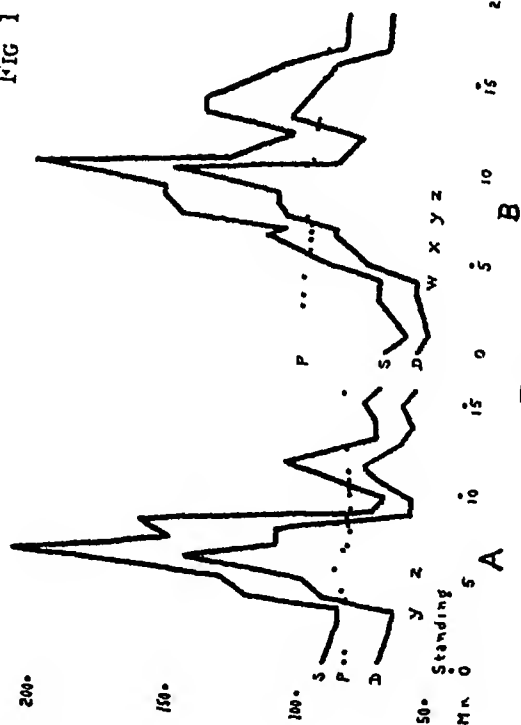


FIG 2

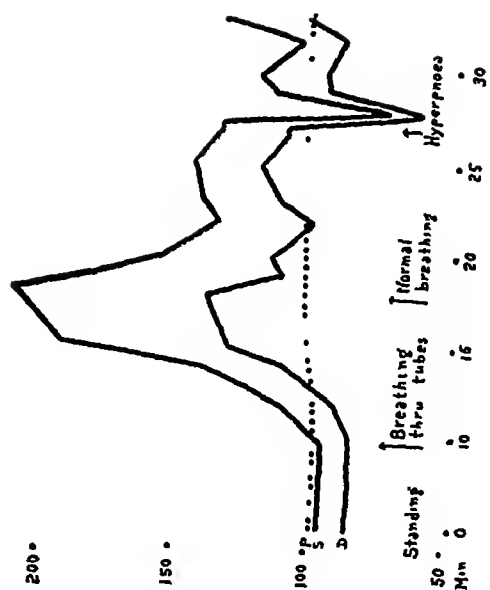


FIG 3

FIG 1 Blood pressure and pulse rate reactions on changing from a recumbent to a standing posture .1 Persistent hypotension .2 Hypotension followed by gradual rise of blood pressure .3 Hypotension followed by rapid rise of blood pressure .4 Absence of hypotensive reaction

FIG 2 Blood pressure and pulse rate reactions on arresting the circulation to active muscles in the standing posture .1 The circulation to the legs was arrested by inflation of cuffs on the thighs at (Y) The cuffs were deflated and the circulation released at (Z) .2 The circulation to the right arm was arrested by inflation of a cuff on the upper arm at (W) The right hand was opened and closed forcefully 10 times at (X) The exercise was repeated at (Y) The cuff was deflated and the circulation released at (Z)

FIG 3 Blood pressure and pulse rate reactions on increasing the alveolar CO_2 and on hyperventilation Where indicated above, the subject began to breathe through two tubes, one meter long and one inch wide After 8½ minutes the tubes were removed and room air breathed in a normal manner Where indicated, the subject then took 10 deep breaths in rapid succession

body) was arrested by compression of the thighs. There ensued a continuous rise of blood pressure from 85 mm Hg systolic and 60 mm diastolic to 210 mm Hg systolic and 145 mm diastolic in two and one-half minutes (figure 2, *a*). Release of the compression was followed by a continuous fall of blood pressure to 70 mm Hg systolic and 60 mm diastolic in five minutes. Blood pressure in the recumbent posture had been 140 mm Hg systolic and 85 mm diastolic.

Arrest of the circulation in the arm produced a similar effect. In the standing posture, blood pressure being 70 mm Hg systolic and 55 mm diastolic, compression of the arm was followed by a rise of pressure to 115 mm Hg systolic and 85 mm diastolic in two and one-half minutes (figure 2, *b*). At this point opening and shutting the hand 10 times caused a further rise to 150 mm Hg systolic and 110 mm diastolic in two minutes. Opening and shutting the hand 10 times more caused an additional rise to 200 mm Hg systolic and 150 mm diastolic in one minute. Release of the compression was followed by a fall of blood pressure to 105 mm Hg systolic and 80 mm diastolic in two minutes, a secondary rise to 140 mm Hg systolic and 105 mm diastolic, and a further fall which reached 85 mm Hg systolic and 70 mm diastolic, seven minutes after deflation of the armlet. These effects were not caused by pain, since no pain was felt in either of the observations described, although it did occur on some of the other occasions when similar results were obtained. In other cases of postural hypotension the same procedure has produced relatively little or no rise in blood pressure^{4, 11, 12}

The subject was then placed in a recumbent posture. Because of the higher blood pressure in this position, the rise produced by arrest of the circulation was less marked. When the subject stood up, arrest of the circulation being maintained, the characteristic fall of pressure was not observed.

In both the standing and recumbent postures, a slight *increase* in heart rate accompanied the *rise* of blood pressure produced by arrest of the circulation. This was in striking contrast to the *increase* in heart rate which accompanied the *fall* of blood pressure produced by standing when the circulation was not arrested. Measured from a continuous electrocardiogram, the rate, recumbent, was 67 (blood pressure 155 mm Hg systolic and 105 mm diastolic), standing, 84 (blood pressure 85 mm Hg systolic and 72 mm diastolic), standing with thighs compressed, 96 (blood pressure 225 mm Hg systolic and 152 mm diastolic).

Sweating was apparent on hot and humid days whenever a high pressure was produced by arrest of the circulation to a limb. When levels of 190 mm Hg systolic and 140 mm diastolic or more were reached, perspiration became conspicuous on the head and body and disappeared promptly when the circulation to the limbs was restored.

Effect of CO₂. The effect of CO₂ was studied in the following manner. The subject was made to breathe continuously through a mouthpiece to which two rubber tubes, one meter long and one inch wide (detached from a Sanborn metabolism spirometer) were connected. He was, therefore, breathing room air through an additional "dead space" of one meter which substantially increased the alveolar CO₂. The following example is typical of the results invariably obtained. In the standing posture, blood pressure being continually about 85 mm Hg systolic and 70 mm diastolic, breathing through the tubes was accompanied by a progressive rise of pressure from 85 mm Hg systolic and 70

mm diastolic to 200 mm Hg systolic and 135 mm diastolic in eight and one-half minutes. Removal of the tubing and resumption of normal breathing was followed by a more gradual return of pressure to the resting level in 15 minutes (figure 3).

In the recumbent posture, the effect of CO_2 was much less pronounced, owing in part to the already high pressure levels. The effect of breathing through the tubes while changing from a recumbent to a standing posture was inconstant. On one occasion, blood pressure fell from 210 mm Hg systolic and 130 mm diastolic to 105 mm systolic and 85 mm diastolic in one minute but rose to 190 mm systolic and 140 mm diastolic in the next three minutes. On another occasion, the pressure did not fall when the standing posture was assumed but instead rose from 170 mm Hg systolic and 115 mm diastolic to 230 mm systolic and 140 mm diastolic in three minutes.

Pulse rate was not significantly affected by CO_2 , although occasionally a slight increase of four to eight beats per minute was noted.

Perspiration appeared over the entire body when the blood pressure was raised to the range of 190/140 mm Hg systolic.

Breathing through the tubes was accompanied by an increase in the rate and depth of respiration. Voluntary hyperpnea without the tubes, however, caused a striking difference in the reaction of the blood pressure (figure 3). In the standing posture, 10 deep respirations in rapid succession were invariably followed by a fall of blood pressure to levels which were frequently unmeasurable. At such times, the subject became too faint to continue standing. Recovery took place within one to two minutes. The procedure did not cause sweating.

Effect of Cooling the Hand With the subject in the standing posture, the hand was immersed in ice water. The initial blood pressure was 110 mm Hg systolic and 85 mm diastolic. Four minutes after the onset of continuous immersion, the blood pressure had risen to 230 mm Hg systolic and 145 mm diastolic and the pulse rate (unlike its reaction to local circulatory arrest) had decreased from 82 to 72. At this point, the hand became numb. Within five minutes more, the blood pressure had fallen to 85 mm Hg systolic and 55 mm diastolic. By this time, the hand was so painful as to necessitate its withdrawal from the ice water and the patient began to perspire profusely, the only occasion on which he did so in the presence of a low blood pressure. Three minutes after removal of the hand from the ice water, blood pressure had risen to 100 mm Hg systolic and 90 mm diastolic and the sweating had stopped (table 1).

Effect of Exercise Starting from the standing posture in which the blood pressure was 70 mm Hg systolic and 60 mm diastolic, the subject walked 14 times over a conventional 18 inch, two step staircase in a period of one minute. Immediately after completion of the exercise, the blood pressure, standing, was only slightly changed, 95 mm Hg systolic and 60 mm diastolic. In the next 90 seconds, however, it rose to 155 mm Hg systolic and 105 mm diastolic, then fell in the next five minutes to 120 mm systolic and 90 mm diastolic (table 1).

Exercise of the upper limb, consisting of opening and shutting the hand forcefully (without previous arrest of the circulation), had no significant effect on the blood pressure.

Effect of Carotid Sinus Pressure In the standing posture, digital pressure over the right carotid sinus produced a fall of blood pressure from 110 mm Hg systolic and 90 mm diastolic to 65 mm systolic and 50 mm diastolic, and the

TABLE I

Blood pressure and pulse rate reactions during various procedures *A* Immersion of the right hand in ice water *B* Walking over two step staircase, fourteen times in one minute
C Digital pressure over the right carotid sinus *D* Inhalation of octyl nitrite

<i>A Effect of cold</i>		
Subject standing	BP 110/85	PR 82
Hand in ice water		
1 minute	135/100	
2 "	170/140	
4 "	230/145	72
6 "	160/110	
7 "	120/95	
9 "	85/55	68
Hand withdrawn from ice water		
3 minutes	100/90	72
<i>B Effect of exercise</i>		
Subject standing	BP 70/60	PR 80
After walking		
1/2 minute	95/60	84
2 "	155/110	80
<i>C Effect of carotid sinus pressure</i>		
Subject standing	BP 110/90	
During C S P	65/50	
After C S P	90/70	
Subject recumbent		PR 66
During C S P		45
After C S P		72
<i>D Effect of nitrite inhalation</i>		
Subject standing	BP 200/135	
During nitrite reaction	75/60	
After recovery	190/140	

subject became extremely faint (table 1) In the recumbent posture, the same procedure caused a fall of blood pressure from 100 mm Hg systolic and 70 mm diastolic to 90 mm systolic and 50 mm diastolic but no discomfort The effect on the heart rate was determined from an electrocardiogram in the recumbent posture Carotid sinus pressure produced slowing of the rate from 66 to 45

Effect of Nitrites Nitrite effect was observed with the subject in the standing posture Two deep inhalations of octyl nitrite were followed by a fall of blood pressure from 200 mm Hg systolic and 135 mm diastolic to 75 mm systolic and 60 mm diastolic in 30 seconds Three minutes after reaching its lowest point, the blood pressure had returned to 190 mm Hg systolic and 140 mm diastolic (table 1) The low pressure was accompanied by slight faintness

Estimation of Peripheral Blood Flow Although quantitative estimates of cardiac output were not obtained, decrease in the stroke and minute volumes of the heart during the periods of hypotension may reasonably be inferred from the low mean and small pulse pressures unaccompanied by any significant cardiac acceleration An indication of the changes in peripheral blood flow was obtained from measurements of the skin temperature of the forehead by means of an electric thermocouple In the recumbent posture, the blood pressure was 115 mm Hg systolic and 75 mm diastolic and skin temperature 93.5° F, on assuming the standing posture, blood pressure fell to 65 mm Hg systolic and 50 mm diastolic and skin temperature fell to 92.2° F, arrest of the circulation to the active forearm was followed by a rise of blood pressure to 200 mm Hg systolic and 135 mm diastolic and a rise of skin temperature to 93.5° F, release of the circulation was followed by a prompt fall of blood pressure and skin temperature to their previous standing levels

A vasodilatation test showed, as a response to heating the body, a rise of skin temperature in the lower extremities of approximately 8 to 10° C in 50 minutes. This reaction was considered normal in time but slightly subnormal in extent and presumably indicative of some degree of obliterative arteriosclerosis.

Relationship of Blood Pressure Changes to Heart Size The heart was observed by fluoroscopy during the changes in blood pressure induced by arrest and release of the circulation to the lower extremities. Although it was anticipated that the cardiac silhouette might increase in size when blood pressure rose and decrease in size as it fell, little if any change could be demonstrated. A more definite change would probably have been detected by graphic methods, such as roentgen kymography, but its relatively minor degree might be predicted by the fact that it escaped direct observation.

Relationship of Blood Pressure Changes to the Electrocardiogram In the standing posture, the electrocardiogram was entirely normal. Rise of blood pressure (induced by compression of the thighs) from 85 mm Hg systolic and 72 mm diastolic to 225 mm systolic and 152 mm diastolic was accompanied by a slight reduction of the T-wave voltage from 0.3 to 0.25 millivolts in Lead I and from 0.4 to 0.3 millivolts in Lead II. In the recumbent posture, the T-waves were inverted in Leads II and III and the electrical axis was normal but shifted toward the right. Thus the changes in the electrocardiogram which accompanied the extreme fluctuations of blood pressure were relatively insignificant.

DISCUSSION

The recurrent complete disappearance of the hypotensive reaction in this case caused the disorder to remain unrecognized for a period of seven years. For the same reason postural hypotension is perhaps frequently unrecognized in other cases. The clinical course in this case also emphasizes a common tendency of postural hypotension toward symptomatic improvement, if not actual recovery. The majority of reported cases have been studied during the height of a malady which, from the descriptions of repeated syncopal attacks, appears almost incompatible with life. The scarcity of autopsy reports or even notation of death under the circumstances is significant.¹ Sleeping in a head up position, which favors concomitant lowering of blood pressure, is apparently a beneficial procedure.¹ Presumably the more prolonged the hypotension, the more effective is the stimulus for the development of whatever compensatory reactions are involved.

The prevailing opinion as to the nature of postural hypotension has been stated by Ellis and Haynes.² "These subjects evidently fail to have reflex vasoconstriction when in a standing position, which would compensate for the increased hydrostatic pressure." On the other hand, MacLean and Allen³ have reported that "recent studies suggest that the defect in postural adaptation is not a defect in arteriolar vasoconstriction but rather one in maintenance of adequate return of venous blood to the heart." The former view seems to offer the more plausible explanation of the observations recorded in the present case. It is very unlikely that simply arresting and releasing the circulation in the forearm could produce such extreme and rapid changes in blood pressure except by means of reflex effects upon the arterioles. The evidence of reduced cardiac output in the presence of hypotension indicates that the return of venous blood

to the heart was diminished. However, the fact that the hypotensive reaction was never accompanied by syncope favors the belief that inadequate arteriolar constriction as well as decreased venous return was involved.

Additional evidence in favor of a defective reflex vasoconstrictor mechanism is the observation that the changes in size of the cardiac silhouette were less than might reasonably be expected if the volume of venous return was the only factor involved in producing the fluctuations in blood pressure. Furthermore sweating in this case disappeared in the presence of hypotension, which is in contrast to the profuse sweating which occurs in normal subjects when venous return is decreased to the point of critically lowering the arterial pressure. Likewise unexplained except by postulating interruption of a reflex mechanism is the failure of the heart to accelerate in the presence of hypotension. Such evidence all points toward inadequate arteriolar constriction rather than inadequate return of venous blood to the heart as the cause of the hypotensive reaction in the case described.

The site and nature of the lesion which interrupted the vasoconstrictor, cardioaccelerator reflex arc in this case are uncertain. The interruption was neither complete nor permanent. It was not complete because at all times it was possible to produce vasoconstriction as an effect of CO_2 or accumulation of muscle metabolites. It was not permanent because the hypotensive syndrome disappeared spontaneously. The most probable explanation is that postulated in other cases of postural hypotension with *tabes dorsalis*, a lesion in the hypothalamic region involving the autonomic reflex center. The rise of blood pressure induced by various procedures would seem to result, under the circumstances, from a "breaking through" of stronger afferent impulses when weaker ones were ineffective. Likewise, the gradual disappearance of the hypotensive syndrome might result either from a progressively increasing number of physiologic afferent impulses or from fluctuations in nerve conductivity at the site of the lesion due to local metabolic changes. An interesting possibility, but one considered by Stead and Ebert⁴ to be potentially unlikely, is that the defect lay, not in the central part of the reflex arc, but in the receptor organs. If this were true, the production of vasoconstriction, either spontaneously or in response to various procedures, would be attributable to the production of chemical stimulation (by CO_2 , metabolites, etc.) sufficient to produce afferent impulses in receptors which for unknown reasons were relatively insensitive.

The relationship between orthostatic hypotension and essential hypertension in this case is noteworthy. The fact that the recumbent blood pressure tended to be relatively high whenever postural hypotension was absent illustrates the distinction between high blood pressure caused by reflex vasoconstriction and that caused by persistently increased vascular tonus in essential hypertension. The blood pressure level was obviously determined by the combined influence of both factors and whenever the factor of reflex vasoconstriction was removed some lowering of blood pressure occurred. The tendency of the blood pressure to return to hypertensive levels is reminiscent of the blood pressure reactions following surgical operations designed to interrupt efferent vasoconstrictor pathways.

It is of interest that the present case exhibited none of the clinical, fluoroscopic or electrocardiographic changes in the heart which are commonly associated with prolonged elevation of blood pressure in spite of the fact that hyper-

tension had undoubtedly been present for at least seven years. Indeed the hypertensive and postural hypotension may have exerted a mutually beneficial effect upon each other. It is not unlikely that the hypertension tended to counteract the consequences of the defective reflex. A comparable case has been observed by Bellet⁹ in which the fall of blood pressure on standing persisted but symptoms decreased in proportion to the progressive development of essential hypertension. Possibly the ultimate symptomatic improvement in many cases of postural hypotension may be owing largely to an added increment of arteriolar tonus.

SUMMARY AND CONCLUSIONS

1 A case of intermittent postural hypotension, associated with hypertension, is described. The hypotensive reaction, because of its inconstancy, was unrecognized for seven years during which time the patient attended medical and heart clinics. It appears likely that for the same reason the disorder is frequently overlooked in other cases.

2 The hypotensive reaction could be abolished by various procedures, such as arresting the circulation to active muscles and increasing the CO₂ content of the inspired air.

3 The observations which were made in this case favor the belief that postural hypotension is caused by a defect of reflex arteriolar constriction.

4 Hypertension may have exerted a beneficial effect as a compensatory influence.

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HODGKIN'S LYMPHOGRANULOMA (RECTAL STRICTURE), REPORT OF A CASE *

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HISTORICAL

PREVIOUS to Schlagenhauser's report of a primary case of Hodgkin's disease of the gastrointestinal tract in 1913 it was a generally accepted rule that the gastrointestinal tract was immune to this disease. Today the literature on this subject and our personal experience make it possible for us to assume that some cases grossly diagnosed as gastric carcinoma, gastric ulcer, enterocolitis, tuberculosis, lymphosarcoma, obstruction of the colon, and carcinoma and syphilis of the rectum may have been intestinal or rectal Hodgkin's disease.

Even though primary and secondary gastrointestinal Hodgkin's disease is definitely known to exist, the meager literature emphasizes the small number of reported cases. Of Hodgkin's stricture of the rectum the writers were able to uncover only two cases, one reported by Gallant and De Vinals and the other given to one of the writers (M G S), by personal communication from B Neiman, former pathologist of the Cook County Hospital, Chicago. The case reported in this paper makes only three cases known to the writers to date.

An impression of the infrequency of the gastrointestinal manifestations of Hodgkin's disease is given by the following investigators. Goldfarb quotes Mead who reported a series of 16,254 autopsies of which 80 were generalized Hodgkin's disease, three were isolated intestinal Hodgkin's and in only one was there secondary involvement of the intestinal tract. Wells and Mayer in 1904 collected 238 cases of pseudoleukemia of which seven were confined principally to the gastrointestinal tract.

ETIOLOGY

The etiology of Hodgkin's disease is still not definitely understood. Sherman in an excellent review of 75 cases quotes Stewart and Dobson who enumerate the different etiologic possibilities: (1) An atypical form of tuberculosis (2) A specific infection due to a diphtheroid bacillus (3) A neoplastic disease (4) A granuloma of unknown etiology. Most investigators favor the latter theory. Lubarsch believes Hodgkin's disease is in an intermediate position between an infectious granuloma and a true tumor. Symmers believes that it is an infection of the hemolytopenetic system.

PATHOLOGY

Terplan divided cases of Hodgkin's disease of the gastrointestinal tract into two groups: (1) Cases in which the gastrointestinal tract is exclusively involved and (2) cases in which the gastrointestinal lesions are part of a generalized or disseminated disease.

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The process may reach the intestinal tract by direct continuity from the involved mesentery, by retrograde lymphatic transport from the mesenteric nodes, or rarely by a primary nodular infiltration of the lymphoid tissue of the submucosa which then protrudes into the lumen or invades the other coats of the bowel. The case communicated to us by B. Neiman was of the primary type involving only the rectum and no other organ. The case which we are reporting is probably secondary to involvement of the mesentery. One can distinguish (1) the ulcerating type of lesion which is more common and consists of numerous ulcers and infiltrations of the stomach or bowel, (2) the tumor-like form which may also be subdivided into (a) nodular infiltrations that involve a small segment, varying in size from that of a pin-head to that of a tangerine, and (b) a more diffuse involvement which produces a stricture of the bowel and is difficult to differentiate from carcinoma or sarcoma. Our case fits into the above classification of Type 2, subdivision "b." The ulcerative type may extend through the various coats of the intestinal wall, perforating into the general peritoneal cavity with resulting peritonitis, or it may produce chronic hemorrhage with an accompanying severe anemia. Other organs may be involved, such as the liver, pancreas, spleen and peritoneum.

In Sherman's series of 73 cases reported in the literature of which 50 were examined post mortem, infiltrations were noted in the liver in 11 and in the spleen in 15. The pancreas was involved in six cases and the lungs in four.

The characteristic microscopic picture is described as a progressive diffuse granulomatous process which involves primarily lymphadenoid tissue. The initial change is hyperplasia of the lymphoid reticulum which is followed by the formation of a peculiar granulation tissue containing a wide variety of cells which replaces the normal architecture. This tissue undergoes necrotic changes and the process terminates with the formation of a hyaline fibrous tissue. The chief characteristic of the cytologic picture is the polymorphous appearance of the tissue, giving it a granulomatous character. The tissue is composed of varying quantities of small and large lymphocytes, reticulum cells, plasma cells, eosinophiles, polymorphonuclear neutrophils, fibroblasts, and mononuclear and multinuclear giant cells (Steinberg and Reed cells). Some cases vary from the classic picture, presenting a complex problem to the pathologist.

SYMPTOMS

The intestinal type of Hodgkin's disease presents one of two varieties of symptoms. (1) the inflammatory variety is accompanied by the passage of blood, bloody mucus, with abdominal pain, meteorism, diarrhea, etc., simulating tuberculous enterocolitis, (2) the obstructive type presents symptoms such as constipation, obstipation, diarrhea, bloody mucus, abdominal cramps or complete obstruction usually simulating carcinoma. Other symptoms of both types are malaise, weakness, loss of weight, loss of appetite, and pruritus ani.

DIAGNOSIS

The diagnosis of intestinal or rectal Hodgkin's disease is made by the biopsy findings, visualization and palpation of a stricture and the roentgenologic evidence of a rectal or colonic filling defect. The microscopic changes at times may be difficult to differentiate from those of lymphosarcoma. The characteristics of

generalized Hodgkin's disease such as enlargement of the lymph nodes, liver and spleen and blood changes may be absent. The roentgenologic changes in Hodgkin's disease of the intestinal tract are not characteristic. Ruggles and Stone state that there is no type of lesion or region characteristic of the disease and therefore there is no specific picture. Very few roentgenologic reports of Hodgkin's disease of the intestinal tract have been reported in the literature. In one of Sherman's cases the roentgenograms showed filling defects which were interpreted as non-specific ulcerative colitis, and simulated intestinal defects seen in patients with tuberculous peritonitis and intestinal malignancy.

DIFFERENTIAL DIAGNOSIS

Hodgkin's disease of the stomach usually simulates gastric carcinoma and gastric ulcer. In the small and large intestine it may resemble enterocolitis and carcinoma and in the recto-sigmoid it simulates lymphopathia venereum, rectal stricture, carcinoma, syphilis, tuberculosis, amebic granuloma, idiopathic ulcerative proctitis and roentgen stricture.

Hodgkin's rectal stricture may consist of varying nodular infiltrations that involve a small segment and vary in size from that of a pin-head to that of a tangerine, or there may be a more diffuse involvement which produces a stricture of the rectum. These nodules may or may not be ulcerated. In our case, the stricture type was present about 7 to 8 cm. above the anal verge. The surface was nodular, granular, ulcerated and beefy in appearance. Bloody mucus was present below the stricture. The stricture lumen admitted the examining finger. The walls were indurated, resilient and of the consistency of sponge rubber. The consistency of the wall was softer than that of carcinoma or lymphopathia venereum. There were no palpable lateral sinuses as felt in lymphopathia venereum, and no ulcerated crater or cauliflower protuberances as felt in carcinoma. The history of previous abdominal Hodgkin's disease and the biopsy helped to establish the diagnosis.

Carcinoma of the rectum, especially the colloid and scirrhous variety with their tubular strictures, can be diagnosed by palpation and biopsy. Although they may occur at any age, they are most frequently seen between the ages of 40 to 60. There is usually a history of change of habit time, rectal bleeding, backache and loss of weight.

Lymphopathia venereum ano-rectal stricture, frequently mistaken in the past for syphilis, is usually found in young colored women between the ages of 25 to 35 and occasionally in white. The percentage in the male is very low. In a series of 138 rectal strictures reported by one of us (M. G. S.) 115 gave a positive Frei test. Of the 115, 90 per cent were negroes, 9 per cent white and 1 per cent Mexican. Ninety-eight of the females were colored, one was Mexican and five were white. There were five male negroes, six male whites and one Mexican. The majority of these strictures are located 4 to 6 cm. from the anal verge. The anal opening is usually patulous. In the ano-rectum the lumen tapers down, giving the appearance of a cone. The lumen is usually tubular, with irregular constrictions and lateral pockets filled with granulation-tissue which easily breaks on digital pressure. These patients are obstipated and void a "cherry-juice-like discharge." The diagnosis is made by the biopsy findings of chronic granulation tissue and a positive Frei test.

Ulcerative proctitis and colitis occasionally produce rectal stenosis of the tubular variety but do not present the cone-like narrowing seen in lymphopathia venereum. There are usually general debility, cachexia, and dysentery of long standing, but the stenosis comes on much later than it does in Hodgkin's disease. The biopsy presents granulation tissue and the Frei test, blood picture and Wassermann reaction are negative.

Amebic granuloma Although rare this condition has been seen by us in three instances and must be considered in the differential diagnosis of rectal strictures. The patient usually passes bloody mucus but little or no pus. Direct smear presents active amebic trophozoites, and the biopsy shows granulation tissue not pathognomonic of Hodgkin's disease.

Tuberculous stricture of the rectum is also rare. David reports three cases although in Graham and Cohen's analysis of 1000 autopsies of which 226 had tuberculosis of the lung, none presented hyperplastic tuberculosis. The scrapings from a positive case should present tubercle bacilli and yeast cells. A good rule to follow is "no lung tuberculosis no rectal tuberculosis."

Post radiation stricture may result following radium and roentgen-ray treatment for carcinoma of the cervix, uterus, prostate, bladder and pelvis. In these cases the stricture is hour-glass in appearance, and the mucosa around the ulcer presents telangiectasis. The biopsy shows granulation tissue. Our patient had had roentgen therapy of the abdomen and pelvis, and a roentgen stricture had to be and was ruled out.

Syphilitic stricture, contrary to popular belief, is also a rare entity. If present in the ulcerative fibrotic stage, there are fibrotic bands palpable between the ulcers instead of nodules and granulomata.

If the ulceration is completely healed one has in reality a healed gumma which presents a healed ring deformity with no blood or pus discharge. There is a history and positive serologic reaction for syphilis. If ulceration does exist the condition responds to anti-syphilitic treatment, which Hodgkin's disease or carcinoma or lymphopathia venereum does not. We have seen only one healed syphilitic ring stricture and one of the ulcerative fibrotic type in 15 years, this includes three years in the Cook County Gastrointestinal Rectal Clinic of Chicago, in which one sees rare and unusual proctologic conditions.

Gonorrhea of the rectum, although commonly present in women, produces few if any rectal strictures. Since the advent of the Frei test many rectal strictures formerly believed to be gonorrheal in origin have been found to be caused by lymphopathia venereum. We have not seen a single case of proved gonorrheal stricture. The case we are reporting in this paper had had gonorrhea and this had to be considered in the differential diagnosis.

Strictures of external origin, such as that seen in carcinoma of the prostate, chordoma, sarcoma, dermoid cysts, Krukenburg tumor in the cul-de-sac of Douglas, cancer of the pelvic organs pressing on the rectum, pelvic abscess, can usually be differentiated from Hodgkin's disease by the absence of ulceration in the mucosa and the elicitation of the above extrinsic pathologic changes. If the intrinsic tumor perforates the rectal mucosa as it sometimes does in carcinoma of the prostate, the biopsy will make the diagnosis.

Rare and benign tumors of the rectum such as fibroma, lipoma, adenoma, angioma, adeno-mioma, fibromyoma of the non-malignant type and sarcoma,

melanoma and leukosarcoma are more or less rare tumors which can produce a rectal stenosis and should be kept in mind. The biopsy makes the diagnosis.

Leukoplakia, although very rare, produces narrowing of the rectum with chronic proctitis.

Lymphosarcoma is characterized by prominent palpable folds of thickened mucosa or rugae. The folds are not fixed and are freely movable on digital examination. The mucosa does not appear ulcerated, and the patient may or may not pass bloody mucus. The condition is rare and has been seen only once by us.

TREATMENT

Roentgen therapy stands out as the most helpful form of treatment as shown by Holmes, Diesser and Camp. Sussig, Singer and others have advocated a combination of resection with roentgen therapy in localized lesions of the gastrointestinal tract. Other palliative measures such as high caloric diet, liver and iron and in certain cases small doses of the arsenicals help to maintain the patient's strength.

PROGNOSIS

Crabber reported 310 cases of Hodgkin's disease, 125 proved by biopsy, 10.3 per cent lived for five or more years following radiation, 16.8 per cent of the proved cases revealed that five year survivors were on the average 10 years younger (34 years of age) than a group that had survived for six months or less. The difference in the period of survival between the two groups is apparently owing to the difference in the virulence of the disease, although the histologic appearance of the nodes showed no correlation. Features which favored good prognosis were localization in one area if combined with early treatment, absence of leukocytosis or leukopenia and gain in weight after irradiation. Fever, marked pruritus and splenomegaly were apparently unfavorable signs.

CASE REPORT

The case is that of a young married woman, aged 24, who was first seen by one of us (H. I. R.) on November 28, 1931. Her only complaint was that of a dry cough of four weeks' duration with no history of any preceding upper respiratory infection. Examination revealed the following: She was somewhat obese and had a slight fever, the tonsils were small with no evidence of infection, the chest findings were grossly negative. She was not seen again until July 9, 1932 (seven months later), when she again complained of a hacking cough.

Examination at this time revealed a slight fever of 100.8° F orally and a small mass palpable in the right supra-clavicular region, as well as enlarged glands in both axillae. A blood count done on July 9, 1932 revealed white blood cells 24,900, neutrophils 80 per cent, small lymphocytes 15, large lymphocytes 1, eosinophiles 2, and red blood cells 4,010,000. The Mantoux test, Wassermann and Kahn tests were negative, as well as agglutination tests for undulant fever. A stereoscopic roentgen-ray of the chest (8/3/32) revealed a moderate amount of fibrosis in both lung fields, the costophrenic and cardio-phrenic angles were clear. A mass the size of a dime was present in the lowermost portion of the right hilus simulating a lymph node. Subsequent blood counts (8/3/32) showed a moderate leukocytosis. White blood cells 22,400, neutrophils 75, small lymphocytes 23, basophiles 2, large lymphocytes 4, with a slight achromia.

The two possible conditions considered at this time were leukemia and Hodgkin's disease. On August 4, 1932 a biopsy of the cervical mass was done and a diagnosis of Hodgkin's lymphogranuloma (atypical) was made by Dr. Israel Davidson, Pathologist at the Mt. Sinai Hospital (figure 1)

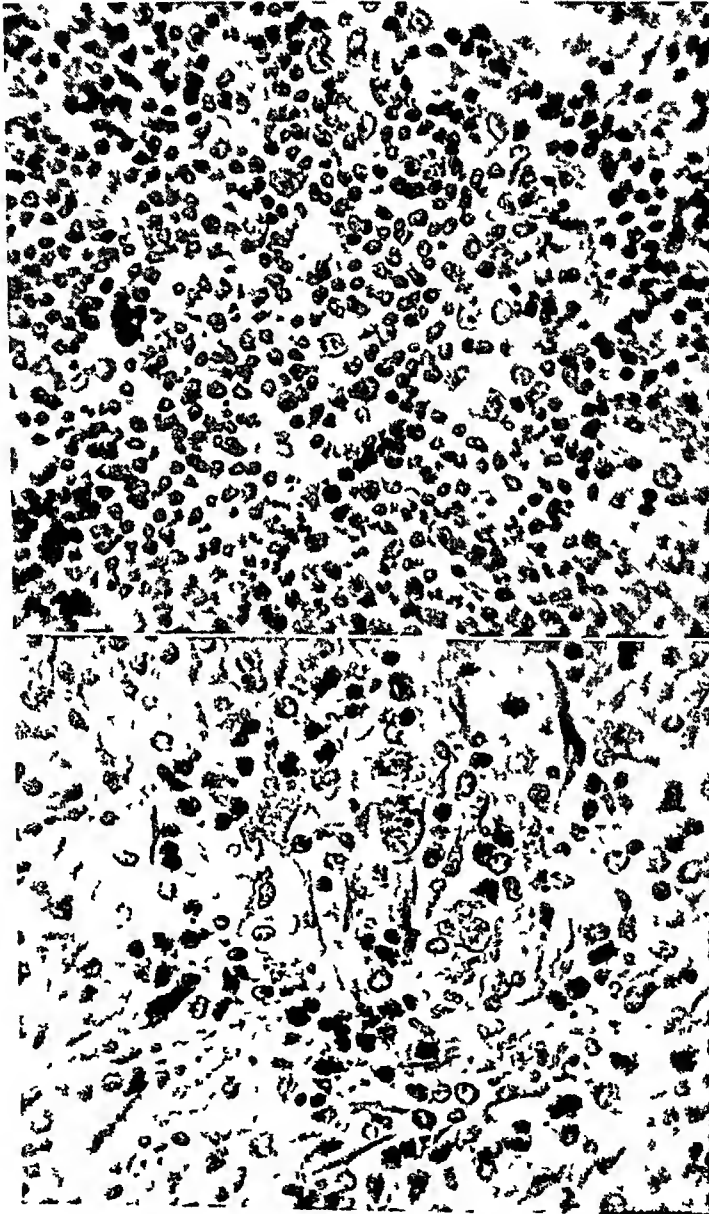


FIG 1 (*above*) Cervical lymph node removed on 8/4/32 showing changes characteristic of early Hodgkin's lymphogranuloma. The normal architecture of the lymph nodes is obscured by a diffuse infiltration with a very clear pleomorphic type of granulation tissue with leukocytes, many of them eosinophilic, with lymphocytes, plasma cells and fibroblasts. The reticulum is thickened, the endothelial cells are markedly swollen. Some of the cells stand out due to the size of their nuclei and some appear to contain several compact nuclei. (High Power $\times 500$)

FIG 2 (*below*) Biopsy taken from peri-renal region removed on 8/23/34 presents a considerably farther advanced stage in the development of Hodgkin's granulomatous tissue. Here the reticulum is much more prominent and the cells are in the background as compared with the preceding figure. Definite small compact giant cells are seen. The granulation tissue has retained its thickened reticulum but lacks its former cellularity. (High Power $\times 500$)

Deep roentgen-ray therapy was prescribed and administered to the neck, sternum, chest and axillae, resulting in the disappearance of the gross lymphadenopathy. During the following summer (1933) she became pregnant and delivered a normal baby

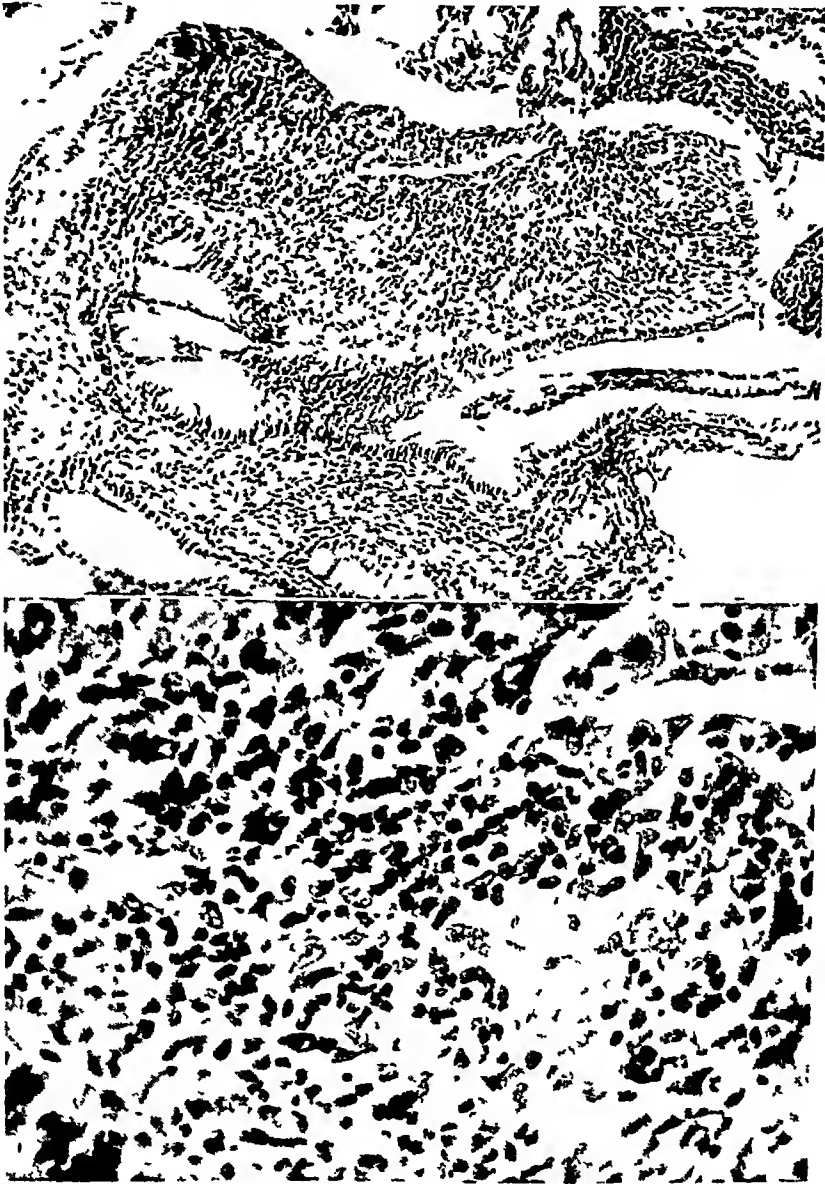


FIG 3 (above) Biopsy section taken from Hodgkin's lymphogranuloma rectal stricture showing rectal mucosa with its accompanying pathological changes (Low Power, H and E stain)

FIG 4 (below) One section of Hodgkin's lymphogranuloma rectal stricture shown in figure 3 visualized under high power, showing lymphocytes, eosinophils, polymorphonuclear leukocytes and occasional giant cell (H and E stain)

girl (May 17, 1934) During her pregnancy she developed a non-pitting edema of the left arm from the axilla to the mid-fingers which remained more or less residual until the end. Her labor and puerperium were moderately febrile, and during the three months postpartum she developed oliguria, increasing pain in the abdomen and left

lumbar region together with progressive edema of the lower extremities. A gastrointestinal roentgen-ray examination on August 14, 1934 failed to reveal any pathological findings.



FIG 5 Mrs F H. Colon enema shows a tubular stricture formation in the rectosigmoid region about four inches long and another in the distal sigmoid region also about four inches long. They both appeared intrinsic. Biopsy established the diagnosis of Hodgkin's lymphogranuloma.

On August 15, 1934, pyelography revealed a non-functioning left kidney. A guinea pig inoculation with a catheterized specimen from the left kidney revealed no evidence of tuberculosis at guinea pig autopsy (10/16/34). Exploration of the left kidney was advised and performed by Dr. H. Rohmick (8/23/34) with the finding of

a mass of glands (weighing several pounds) compressing the left kidney and ureter and extending down into the pelvic region. The mass and kidney capsule were freed to some extent and a biopsy (No 2) was taken, which specimen corroborated the previous diagnosis of Hodgkin's lymphogranuloma (Dr I Davidson) (Figure 2).

Deep roentgen-ray therapy in repeated courses followed with clinical improvement and gain in weight up to 147 lbs. The recurrent enlargement of the glands in the abdomen, suprapubic and pelvic regions responded to the successive series of deep roentgen-ray therapy with resultant well being of the patient. Supportive therapy of high caloric diet along with liver and iron helped in maintaining the patient's strength during a period of eight years. During the last year, however, progressive bowel discomfort developed with frequent muco-sanguinous stools and marked tenesmus, alternating with obstipation. A rectal examination (by H I R) in March 1939 revealed a firm infiltrated constriction ring in the rectal ampulla about four inches above the anal opening, which barely permitted the passage of the examining finger. Concentration of deep roentgen-ray therapy over this region was advised and carried out with little improvement of the rectal symptoms. On September 19 and 21, 1939, proctoscopic examinations were done by one of us (M G S) and biopsy specimens were removed with the diathermy cutting current directly from the infiltrated area in the rectum. The pathological report revealed "mucous membrane with regular glands and dense areas of infiltrating round cells and eosinophilic polymorphonuclears. Submucosa and muscularis similarly infiltrated. There are a few scattered large epithelial cells which with the eosinophiles suggest Hodgkin's lymphogranuloma" (Dr I Pilot) (Figures 3 and 4).

A barium roentgen-ray of the colon done shortly after the biopsy revealed the presence of constriction rings in the rectal and sigmoid regions (figure 5). The question that presented itself was, were these strictures in the sigmoid and rectum possibly due to the resultant fibrosis from the intense deep roentgen-ray therapy she had previously received or was it part of the generalized Hodgkin's disease process infiltrating the sigmoid and rectum? From the results of the proctoscopic examination and biopsy findings we feel justified in concluding that the strictures of the rectum and sigmoid were part of the Hodgkin's disease process infiltrating and extending from the previously described abdominal and pelvic lesions. Further roentgen-ray therapy and supportive treatment were administered. The patient again improved for several weeks, but this was followed by a progressively downward course. During the last months of the patient's illness there was continued fever, lack of appetite and inability to eat or drink without experiencing prompt abdominal pain, tenesmus and frequent muco-sanguinous stools. There followed progressive wasting with terminal bronchial congestion. The patient died on January 11, 1940, more than eight years after the first appearance of symptoms. An autopsy could not be obtained.

CONCLUSIONS

- 1 Hodgkin's lymphogranuloma of the gastrointestinal tract is comparatively uncommon.
- 2 Hodgkin's lymphogranuloma of the rectum is very rare. A case is reported herewith which is only the third definite one discovered in the literature and by personal investigation.
- 3 A differential diagnosis of rectal strictures is discussed.

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A CASE OF MARKED TORTUOSITY OF THE ABDOMINAL AORTA WITHOUT CALCIFICATION, CAUSING MILD ATTACKS OF SUBACUTE INTESTINAL OBSTRUCTION *

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THE consensus of present medical opinion is that atherosclerosis of the aorta is most marked in the abdominal portion and that it rarely if ever gives rise to clinical symptoms. This opinion is unanimously expressed in the recent textbooks consulted.¹ One encounters patients with marked general atherosclerosis of the large vessels complaining of various irregular digestive symptoms, various aches and pains, paresthesias, loss of weight and often mental retardation. Such patients seem to exemplify the results of advanced general senile changes rather than specific localizations, accompanied by rather than due to the atherosclerosis. Some authors have held that digestive disorders are due to abdominal sclerosis with narrowing of the blood vessels, whereas others² have ascribed pain and stiffness in the back to ischemia resulting from calcareous disease of the dorsolumbar aorta.

In the past older authors referred to angina abdominis (Pal, Brunton, Allbutt) and "angina pectoris pseudo-gastralgique" (Huchard). Goodman³ refers to these authors and presents the case of an 82 year old female who, follow-

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ing hard physical work, was stricken with umbilical pain accompanied by great anxiety, nervousness and restlessness, promptly relieved by inhalation of amyl nitrite. Attacks of coronary insufficiency, presumably due to myocardial ischemia, may be represented by pain in the abdomen. On the whole, it is unlikely that specific abdominal pain due to atherosclerosis in the abdominal aorta or its branches occurs except as the result of acute ischemia due to either mesenteric thrombosis or dissecting aneurysm. The case reported herewith is interesting because the abdominal aorta was unusually tortuous, without calcification, and resulted in mild attacks of subacute intestinal obstruction due to pressure on the left portion of the transverse colon.

CASE REPORT

A male architect was first seen one year and eight months before the last observation. He was without complaints, except for mild fatigue. Albuminuria had been discovered 10 years previously. His father died of heart disease at 67. His mother died of old age at 84. One sister died of heart disease at 67. The history otherwise was not contributory.

Physical examination showed tortuous arterioles in the fundi with arteriovenous compression. The heart was enlarged 1 cm to the left. The blood pressure was 175 mm Hg systolic and 120 mm diastolic. A slight to moderate grade II systolic murmur was heard at the apex and along the left sternal border in the second and third interspaces. The percussion note was slightly dull at the apices with increased whispered voice in the paravertebral regions on both sides at the level of the spine of the scapulae. The remainder of the physical examination was negative, except for the feature of greatest interest, which was a large, easily palpable pulsating mass far to the left in the loin, which could easily be followed as it curved back toward the midline and over the pelvic brim slightly to the right of the midline. Orthodiagram showed a tortuous thoracic aorta and slight prominence in the region of the left ventricle. The total transverse diameter of the heart was 11.5 cm. The internal thoracic diameter was 22.7 cm. The electrocardiogram showed normal rhythm, rate of 80, with shallow inversion of T_1 and late inversion of T_2 and T_F . The maximum urine concentration on limitation of fluid (Fishberg technic) reached 1016. Examination of specimens showed none up to a trace of albumin. Various sediments showed a rare to an occasional red cell and none to many granular casts. Intravenous phenolsulphonphthalein showed an excretion of 10 per cent in 15 minutes, 15 per cent in half an hour, and 20 per cent in one hour. The nonprotein nitrogen was 38 mg per cent of whole blood.

The diagnosis was hypertensive and arteriosclerotic (coronary) heart disease, chronic vascular nephritis, hypertension. No special treatment was advised except for general hygienic directions and a moderate protein diet without added salt.

The patient had felt well for a year and a half when, two months before the last observation, he complained of a heavy feeling, or "lump" in the left lower quadrant and across the lower abdomen, coming on five or six hours after heavy meals, followed by constipation and gradual recovery in the course of 24 hours or less. With the attacks there was considerable belching of gas, but no passing of flatus. Physical examination showed rather marked arteriovenous compression in the arterioles of the fundi, and caliber changes were apparent. The heart appeared to be enlarged as before. When the blood pressure was taken no sounds could be heard on auscultation and the systolic pressure had to be estimated by palpation. The pulsating mass considered to be the abdominal aorta was even farther to the left and felt larger. There seemed to be no essential change in his condition, except that the arteriolar sclerosis noted in the fundi seemed more advanced, as did that of the brachial arteries as compared with the initial observation a year and a half before. It was thought

probable that the tortuous abdominal aorta exerted some extrinsic pressure upon the large bowel and was causing mild attacks of subacute intestinal obstruction. Careful roentgen examination with the barium enema showed a rounded defect in the left side of the transverse colon due to a pulsating mass. The defect was persistent throughout the examination and was checked on a later occasion. There was no evidence of



FIG 1 A retouched photograph of the original roentgen-ray plate showing a markedly tortuous abdominal aorta, the outlines of which were easily recognized on the original radiograph. The persistent defect in the left portion of the transverse colon caused by the aorta is easily apparent.

intrinsic disease (figure 1). There was no evidence of microscopic blood in the stools. The remainder of the laboratory examination was essentially as before, showing a moderate degree of failure in concentrating power and in delayed excretion of the intravenous phenolsulphonphthalein.

Mineral oil and a low residue diet divided into five small meals relieved the symptoms for the remaining two years of his life, terminated by a cerebral accident at a distance, so that no autopsy was obtained

SUMMARY

A case is presented which showed marked tortuosity of the abdominal aorta without calcification, resulting in mild attacks of subacute intestinal obstruction

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namely, anatomy, physiology and pathology, combined with years of experience in the sick room and at the autopsy table

Of all the fine teachers with whom I have been privileged to work, Professor Kovacs of Vienna stands preeminent as a diagnostician. The thoroughness with which he made his examinations and the finesse with which he correlated salient points in the history to his positive objective findings, together with the pathological changes that must occur as a result of organic lesions, was an inspiration never to be forgotten. The utter accuracy of his diagnosis, as demonstrated at the autopsy table, was phenomenal to all who worked with him. This was all the more remarkable because he did not have access to modern blood chemistry, the electrocardiograph or the other laboratory tools upon which we depend so much today.

Lessons learned under such a teacher are seldom forgotten, but too often neglected because of too many modern tools which give us positive findings in shorter time and with less expenditure of energy (by tools, I mean all the modern laboratory methods and appliances). We cannot do without the tools, but neither should we rely exclusively on them.

Genius has been defined as "the capacity for taking infinite pains." Few of us can hope to be Oslers, Janeways, Neussers or Kovacs, but who cannot improve by experience and practice? It is amazing to what degree these two things, experience and practice, can train our special senses. Paderewski, Heifetz, or any other great genius in any other field found no short cut to the technic that gave him fame. Only by the same kind of hard work and diligent practice can the physician hope to develop a knowledge and skill that will insure for him accuracy in physical diagnosis.

Some may train one sense more than others. Professor von Neusser's acuity of smell was so pronounced that he frequently diagnosed a case on the odor of perspiration. He would walk into a ward of the general hospital in Vienna, lift a patient's arm, sniff, and name the malady, then he would proceed with a thorough examination and discussion from every possible point of view. Rarely was his first impression proved wrong by the exhaustive study. But even von Neusser was never guilty of relying only on this one remarkable capacity. Much less should those of more limited experience attempt snapshot diagnosis.

The well-known Dr. Babcock of Chicago reached an enviable position as diagnostician and teacher of internal medicine, though totally blind. This was possible by training the other senses to compensate for this total absence of sight. Our own Dr. Pottenger can detect lesions in the chest by palpation alone, so keenly is his sense of touch developed. However, it is not the development of great skill in the use of a single sense, but the training of all the senses that makes for ability in physical diagnosis. Probably no other single factor has contributed as much to the high mortality in the oral tests as has this inability to make a satisfactory physical examination.

Some of the observations made at the time of the examinations may be of interest to you. It is impossible to enumerate them all or to classify

them as to their frequency. Some candidates do not do themselves justice because of extreme nervousness. This is a condition that is inherent with some individuals throughout life. Many are inclined to make a tentative diagnosis from a lead obtained in the history and are apt to concentrate too much upon that part of the body suggested by this lead and neglect the rest of the patient. They forget how much can be learned by a thorough inspection and even palpation of the entire body and that this takes actually a short time when compared with the knowledge thus obtained. Some forget that many valuable clues may come from the general appearance of the patient—his expression, his mannerisms, the character of the skin and the mucous membranes, as well as the hair and even the fingernails.

It is gratifying to see the large number of candidates who use the ophthalmoscope as part of their general examination. Their interpretation of what they see is not always correct.

Fortunately the popularity of vitamins and the frequency with which avitaminosis occurs has made the inspection of the mouth and tongue almost as common now as when "stick out your tongue" was the first and sometimes the extent to which physical diagnosis was practiced in our grandfathers' day. In spite of this, many candidates overlook lesions of the tongue which could give them a very positive clue toward a correct diagnosis.

In the examination of the neck very few doctors ever feel for Virchow's gland. Some have overlooked a goiter because of its being partially sub-sternal. Such prominent findings as distended and even pulsating veins are missed because of careless inspection.

An examination of the chest is one of the best of all criteria by which one can be judged as to his capability to make a physical diagnosis. Lack of knowledge of the normal anatomy, with particular reference to the heart and lungs and their relation to the chest wall, is a common fault. Those who fail to note the shape, contour, symmetry and expansion of the chest are usually the ones who overlook important pathology within the chest. Those who chart their findings with a skin pencil on the chest generally make more careful and accurate examinations because they realize that they have left their "writing on the wall." Unfortunately, very few use this method.

In making diagnoses of cardiac conditions too little attention is given to the pathological changes that must occur as a result of organic lesions in the heart. Much valuable information can be discovered by careful examination of the pulse, the neck veins, the lungs and the liver, accurate outlining of the heart borders with light percussion and the aid of a small tuning fork in difficult cases, and lastly, by palpation of the cardiac impulse. All this should be done before resorting to the stethoscope for a diagnosis. Most candidates look at you in bewilderment when you ask them to tell you whether the impulse felt through the chest wall is from the right or left ventricle because they have forgotten, or never learned, the relative position of the two ventricles to the anterior chest wall.

So much reliance is placed upon roentgenograms that very few can outline the heart borders accurately, and I am still old-fashioned enough to think that all well-trained men should be able to do this without access to roentgen-ray in a large percentage of the cases, provided that they learn to percuss lightly and parallel to rather than across the heart border.

Too many candidates are dependent upon the electrocardiogram for their diagnosis. This is particularly true in cardiac arrhythmias. Of course, we all want and need the electrocardiogram for certainty of diagnosis, but we should not become so dependent on it that we are lost without it. Many who read the electrocardiogram well make poor physical examinations of the heart.

Lesions of the lungs are just as frequently overlooked or misinterpreted as those of the heart. It is not essential that one recognize all the signs by their specific titles, that is, the name of the man who discovered them, but it is essential that he recognize their existence and be able to interpret their significance. He should be able to distinguish between a pneumonia of the left lower lobe and a compression of this lobe by an enlarged heart, even if he doesn't know that it is called an Ewart's sign.

As intimated before, the old clinicians displayed their skill more in their examination of the chest than any other part of the body, but today some of the poorest examinations have been made by candidates who have confined their work to diseases of the chest. A probable explanation of this was given to us in Boston last year by an authority on tuberculosis who said that they do not rely much on physical examination nowadays, but rather upon the roentgenograms. To the expert this is a short cut to diagnosis, but to those of lesser experience it is a dangerous procedure.

Lack of thoroughness in examination of the abdomen is just as noticeable as in that of the chest. In Cleveland last year two different men made a diagnosis of pernicious anemia in a thin, pale woman, from her blood picture, and completely failed to see vigorous peristalsis and even antiperistalsis of the stomach. They were very much embarrassed when this condition was made obvious to them by a little gentle tapping of the abdomen.

These younger men seldom attempt to detect the old-fashioned splash in the stomach as an indication of a probable obstructive lesion at the pylorus. The accuracy with which gastrointestinal diagnosis can be made by roentgen-ray has made many ignore the technique of the old clinician in their examination of the abdomen. In fact, few of the younger men even know what Murphy's sign of gall-bladder disease is. Also, many forget that more can be learned by gentle palpation than by deep and rough probing of the abdomen. Some are too hesitant to make a diagnosis of intra-abdominal pathology, particularly inflammatory, such as appendicitis, without the support of positive laboratory findings. They do not realize that an acutely inflamed appendix can progress to perforation without a leukocytosis or even a rise in temperature.

Peripheral vascular lesions are sometimes missed by superficial examination of the extremities. In one instance a coarctation of the aorta would have been detected had the doctor taken the trouble to take the blood pressure of the leg or had he even compared the pulse of the upper and lower extremity.

The use of the Wassermann test has so relegated the necessity for seeking external physical signs of syphilis that few younger doctors know where to feel for tibial nodes and occasionally miss very obvious visible manifestations of the disease.

Again, too many candidates are lost when their clinical case involves diagnostic problems in neurology. They also fail to appreciate the close relationship which exists between the nervous system and all the functions of the body.

An observation made and commented on by all the Board members is that on the whole the candidates that make the poorest showing of any group are the ones who have gone too early into subspecialties before sufficient practice in the broad field of internal medicine.

Apropos of what has been said of the candidates for the American Board examinations, I might add that it is true to a greater degree of our interns and residents in our hospitals. A letter received the day I left home from another Board member reads in part, "My observations relative to the inadequacy of physical diagnosis are most concrete. In a word, the young internist has been trained out of physical methods by the attitude of his teachers or the sense of inadequacy in his own efficiency. For example, this last week a superior resident, a graduate of one of our top medical schools, termed a cardiac lesion that of mitral stenosis. A glance at the thorax and percussion of the borders of the heart refuted this diagnosis. When confronted with his statement that my method, while confirmed, smacked of snap diagnosis, I called his attention to the fact that there was a diffuse apical impulse in the sixth interspace in the left anterior axillary line and the enlargement was intracardial since the right border of cardiac dullness was not displaced to the left, hence a pure mitral stenosis could not possibly account for the contour of the heart. When impressed by the directness of my logic he retorted, 'Well, I would have picked it up on the orthodiagram anyway.' I believe we are approaching what S. Weir Mitchell termed, 'de-mentalization by mechanical gadgets'."

It is surprising and disquieting that as high as 30 per cent of the examinees fail in some phase of the practical examination and not wholly through fault of their own. Is it not a reflection upon the modern teaching in our schools today, and should not revision in the plan of teaching be made so that more emphasis be given to proper technic and to the importance of physical diagnosis in our medical education of students and later internes?

One of the very best types of training that any doctor can get before he attempts to specialize in any field is a few years in general practice, provided he has been well trained before he leaves the supervision of his teachers.

In fact, a year or two in a rural community, where a man is wholly dependent on his own resources, might be a good substitute for one of the three years' training in a hospital that we require of our candidates today. Such a program would be specially valuable if post-war conditions require a geographical redistribution of medical personnel.

In conclusion, we must appreciate and utilize the countless advantages of all the modern achievements in the advancement of medicine today. I merely want to make an urgent appeal that the old-fashioned art of physical diagnosis be not neglected or set aside for the newer methods, but that both may travel along hand in hand.

G GILL RICHARDS

REVIEWS

Thoracic Surgery By CHARLES W LESTER, A B, M D, F A C S 141 pages, 22 X 14.5 cm Oxford University Press, New York 1941 Price, \$2.00

This outline conforms in its general plan with corresponding outlines on other subjects. It will be of use chiefly to those who already have a fair knowledge of the subject, but for such it should be useful as a means of quick review.

Certain statements in the outline are open to criticism. In places clarity and precise accuracy have been sacrificed for brevity. Thus, the description of the reflection of the pericardium onto the chest wall (page 6, A 1) appears misleading anatomically. The "obliterated ductus arteriosus extends from the pulmonary artery to the arch of the aorta" opposite rather than "at the origin of the subclavian artery." (Page 7, B 1 c) The description of the procedure for inducing artificial pneumothorax (page 106, E 2 d) might lead the inexperienced to believe that the water entered the pleural cavity.

Certain details of technic may also be questioned. The use of needle punctures or incisions in treating subcutaneous emphysema (page 30, C 2) is so rarely justified that mention of it seems out of place in such an outline. The same may be said of aspiration of the pericardial cavity by the posterior approach, and of inducing pneumothorax under positive pressure. The minimum of two years and maximum of five years for maintenance of artificial pneumothorax are usually regarded as too short. Cessation of symptoms, failure to demonstrate tubercle bacilli in the sputum, and roentgenographic evidence of healing are not reliable indications for abandoning pneumothorax treatments (page 108).

The technic described for operation on diverticula of the esophagus (page 49) and the position recommended for operation on the phrenic nerve (page 101, D 1) may also be questioned.

In spite of such points, the work is well done, and it should serve a useful purpose.
O C B

Gynecological Operations By J LYLE CAMERON, M D, F R C S (ENG), F A C S, M R C O G 200 pages, 22 X 14 cm Oxford University Press, New York 1941 Price, \$5.50

Dr Cameron should be complimented for his very clear and concise treatment of a field as broad as gynecological operations. The text is very well arranged, with bold face type liberally used to indicate the more important topics. The subjects are adequately discussed, without being voluminous. The illustrations are exceptionally well done, and are for the most part complete in detail.

The book should be classified as an excellent handbook of a very extensive subject.
W K D

Directory of Medical Specialists Certified by American Boards Directing Editor PAUL TITUS, M D 2495 pages, 23.5 X 16 cm Columbia University Press, New York 1942 Price, \$7.00

This large volume contains a complete list of all diplomates of the American Boards of each of the fifteen major specialties, about 18,000 in all, certified prior to January 1, 1942, 4,000 more than were included in the first edition. These are first listed alphabetically under each specialty, subdivided by states and cities, with a brief biographical paragraph. There is a second general alphabetical list of all diplomates, giving only the address and specialty of each.

There is a list of the members of the Advisory Board for Medical Specialties and of each American Board. There is also a brief historical account of the organization of each board, its purposes, and the qualifications required and procedure necessary to secure certification. A list of the national and sectional societies is given under each specialty.

This is a valuable book of reference, indispensable for every school and hospital library and a useful addition to that of every physician.

P W C

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members

Books

- Dr Harold E B Pardee, F A C P, New York, N Y—"Clinical Aspects of the Electrocardiogram",
Dr Maurice A Schnitker (Associate), Toledo, Ohio—"The Electrocardiogram in Congenital Cardiac Disease" and "The Sulfonamide Compounds in the Treatment of Infections",
Dr Noble P Sherwood, F A C P, Lawrence, Kan—"Laboratory Exercises in Bacteriology and Diagnostic Methods" and "Immunology",
Dr Russell M Wilder, F A C P, Rochester, Minn—"A Primer for Diabetic Patients"

Reprints

- Dr Archibald A Barron, F A C P, Charlotte, N C—2 reprints,
Dr Charles J Bartlett, F A C P, New Haven, Conn—1 reprint,
J Edward Berk (Associate), Lieutenant (MRC), U S Army—2 reprints,
Dr Abner M Fuchs (Associate), New York, N Y—1 reprint,
Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
Dr John S Hibben (Associate), Pasadena, Calif—1 reprint,
Dr Saul Jarcho (Associate), New York, N Y—1 reprint,
Dr Robert C Kirk (Associate), Columbus, Ohio—1 reprint,
Dr Hugh R Leavell, F A C P, Louisville, Ky—1 reprint,
Dr William M LeFevie, F A C P, Muskegon, Mich—1 reprint,
Dr Aleksei A Leonidoff, F A C P, Poughkeepsie, N Y—1 reprint,
Dr Harry Mandelbaum, F A C P, Brooklyn, N Y—2 reprints,
Dr Thomas H McGavack, F A C P, New York, N Y—2 reprints,
Dr Rollin H Moser, F A C P, Indianapolis, Ind—2 reprints,
Dr William D Nimeh, F A C P, Mexico City, Mexico—1 reprint,
Dr Henry I Shahon, F A C P, Aspinwall, Pa—1 reprint,
Dr R Henry Temple (Associate), Kinston, N C—2 reprints,
Dr Harry B Thomas, F A C P, York, Pa—1 reprint

Dr Julian M Ruffin, F A C P, Durham, N C, Recorder of the American Gastroenterological Association, has donated copies of the Transactions, 1927 to 1934, 1937 and 1939, of the Association to the College Library. Many of the articles published in the Transactions are by Fellows of the College.

COLLEGE WAIVES DUES AND REDUCES FEES TO MINIMUM OF MEMBERS SERVING IN THE ARMED FORCES

On April 21 1942, the Board of Regents adopted the following resolutions

BE IT RESOLVED, in view of the present emergency, all members, Associates and Fellows, of the American College of Physicians who are called to active military duty with the armed forces be accorded waiver of dues during their period of active service and complete detachment from private practice, such waiver to be operative from January 1, 1942

Such members shall inform the Executive Secretary of the date of entrance upon military duty and of the date of discharge therefrom

In view of the necessary changing locations of these members and the inherent difficulty of supplying the ANNALS OF INTERNAL MEDICINE, the journal and other publications shall not be furnished

BE IT FURTHER RESOLVED, the initiation fee of members serving with the armed forces be reduced to ten dollars

The Executive Secretary has already taken appropriate steps to put this new regulation into effect. Any members who have very recently entered the armed forces, but have not communicated advice to the College Headquarters, should write immediately to Mr E R Loveland, Executive Secretary, 4200 Pine St, Philadelphia, Pa

ACTING GOVERNORS TO BE APPOINTED TO SERVE DURING ABSENCE OF REGULAR GOVERNORS ON MILITARY DUTY

By special action of the Board of Regents of the American College of Physicians, April 21, 1942, the Executive Committee of the College is empowered to designate an "Acting Governor" for any State, Province or territory, on notification of a Governor that he is called to active service in the armed forces and will be unable to serve during the emergency. It was pointed out that as long as a Governor can serve adequately, even though on active duty, he may continue so to serve. When, however, the Governor feels he cannot properly serve, he shall notify the Executive Offices of the College and he may, further, suggest the name, or names, of an Acting Governor. The Acting Governor appointed by the Executive Committee shall serve only until the regular Governor shall be available actively to serve again.

Dr Patrick L Ledwidge, F A C P, Detroit, Mich, has been appointed Acting Governor for Michigan by the Executive Committee of the College, to serve during the absence of the regular Governor, Dr Douglas Donald, F A C P, who left for active duty in the armed forces on July 15, 1942

Dr Joseph L Lilienthal, Jr, Baltimore, Md, has resigned the Research Fellowship awarded by the American College of Physicians, because of being called to active duty in the U S Army. This Fellowship was granted for the period September 1, 1942, through August 31, 1943, for work under the direction of Dr A M Harvey in the Department of Medicine of Vanderbilt University School of Medicine, Nashville, Tenn, the work to be concerned with observations on myasthenia gravis and related problems in neuromuscular transmission in man

At the recent meeting of the American Medical Association at Atlantic City, N J, Dr James E Paullin, of Atlanta, was elected President-Elect of the American Medical Association. Dr Paullin was the only nominee.

Dr Paullin requested that he be relieved of his membership on the Council of Scientific Assembly, and subsequently Dr Edward L Bortz, F A C P, of Philadelphia, was appointed to fill Dr Paullin's unexpired term, ending in 1943

Dr Emanuel Libman, F A C P, of New York City was awarded a silver medal for his exhibit illustrating Endocarditis and "Libman-Sacks Disease" at the Atlantic City meeting of the American Medical Association during June

Captain Frederick Ceres (MC), U S N, F A C P, was detached from the U S Naval Air Station, Pensacola, Fla, June 23, 1942, for aviation duty elsewhere. Since

June, 1939, Captain Ceres had been in charge of the Medical Department and the School of Aviation Medicine. The establishment of this School came at a most propitious time when, because of the demands of the National emergency, it became necessary to train many medical officers as flight surgeons and aviation medical examiners. The Naval School of Aviation Medicine is a monument to his foresight, his courage and his organizing ability.

The medical officers of the Air Station, Pensacola, tendered Captain Ceres a farewell party on June 19, at which time the Commandant presented him with the first official Flight Surgeon's Insignia authorized by the United States Navy Department in Washington.

Dr. J. J. Singer, F. A. C. P., has been appointed Medical Director of the Los Angeles Sanatorium, ushering in broadened activities in the field of tuberculosis education, prevention, research and patient rehabilitation. The Los Angeles Sanatorium is a national non-sectarian hospital which has cared for over 10,000 indigent tuberculous patients in its thirty years of service.

Dr. Singer formerly was Associate Professor of Clinical Medicine at Washington University School of Medicine, St. Louis, and was in charge of the medical and surgical chest service at Barnes Hospital. In 1937 he removed to Los Angeles and since that time has been Associate Clinical Professor of Medicine at the University of Southern California School of Medicine, Medical Director of the Rose Lampert Graff Foundation, and Consultant in Diseases of the Chest in several local institutions.

UNITED STATES PUBLIC HEALTH SERVICE

Owing to the increasing number of war connected activities, the Surgeon General of the U. S. Public Health Service has commissioned a number of physicians in the U. S. Public Health Service Reserve for full-time service in critical areas in the United States, whose commissions will terminate at the conclusion of the war. In addition, it is planned shortly to commission 2,100 additional Reserve Officers, most of whom will be retained on an inactive status, but be subject to call for full-time service in emergency Base Hospitals in the interior and in reception areas for the duration of the war, in the event it should become necessary to evacuate civilian hospitals and civilian population.

Reserve Officers in the Public Health Service assigned to field duty receive the pay, rank and allowances equivalent to those of the armed forces. While on active duty in the field, they wear the uniform of the Army, except for the Corps insignia. The titles in the Public Health Service range from Assistant Surgeon, with the rank equivalent to First Lieutenant, to that of Medical Director, with the rank, pay and allowances of Colonel. Services rendered by these Reserve Officers of the U. S. Public Health Service are comparable to those of Officers in the Army and Navy, including assignment by the Surgeon General to service outside of the continental limits of the United States.

Dr. Lewis J. Moorman, F. A. C. P., Oklahoma City, Okla., has been named President-Elect of the National Tuberculosis Association.

John W. Shuman, Sr., F. A. C. P., Lieutenant Colonel (MRC), U. S. Army, previously and for a long time in practice at Santa Monica, Calif., has recently been transferred from Camp Lockett, Calif., to become the Chief Medical Officer of the station hospital at Camp Adair, Ore.

Dr Salvatore Lojacono, F A C P, Howell, Mich, was recently appointed Superintendent and Medical Director of the Jackson County Sanatorium, Jackson, Mich

At the recent annual meeting of the American Association for the Study of Allergy in Atlantic City, N J, Dr Samuel M Feinberg, F A C P, Chicago, Ill, was named President, Dr Oscar Swineford, Jr, F A C P, University, Va, President Elect, Dr Karl D Figley, F A C P, Toledo, Ohio, Vice-President, and Dr J Harvey Black, F A C P, Dallas, Texas, Secretary-Treasurer

Dr Marjorie E Reed, F A C P, Plymouth, Pa, has been appointed Director of Woman Physicians of the Medical and Surgical Relief Committee of America Dr Reed became affiliated with the Committee last February Since that time she has built up in Luzerne County (Pa) an active group of women physicians who have sent quantities of medical supplies and contributions to the Committee headquarters

Dr Walter C Smallwood (Associate), who was on active duty as a Lieutenant Commander in the Medical Corps of the U S Navy from December 17, 1941, has been placed on inactive duty because of a minor physical incapacitation He resumed private practice at Long Beach, Calif, on July 15

The American Physicians' Art Association held its 5th annual exhibition at Atlantic City, N J, June 8-12, 1942 There were 350 original art works displayed, and 73 prizes were awarded Among the recipients were the following members of the College

- Dr Nils P Larsen, F A C P, Honolulu, T H—a cup for his etching "Heil",
 - Dr Louis L Perkel, F A C P, Jersey City, N J—a medal for his photograph, "Peggy's Cove",
 - Dr George E Pfahler, F A C P, Philadelphia, Pa—a medal for his hand-colored photograph, "Prince II",
 - Dr Leo Risen (Associate), Portland, Ore—a medal for his oil painting "A Study in Drapery"
-

Dr Edgar W Norris, Jr (Associate), U S Public Health Service, participated in a symposium on "Venereal Diseases" at the 22nd Annual Health Conference of the State Department of Health in Baltimore, Md, May 15-16

Dr Robert F Loeb, F A C P, New York, N Y, has been named Lambert Professor of Medicine at Columbia University College of Physicians and Surgeons Dr Loeb is the first incumbent of the Chair, which was established in honor of the late Dr Samuel Waldron Lambert, F A C P

The Twin Lakes District Medical Society of Iowa held its 20th Annual Assembly at Rockwell City, June 25 Dr Thomas J Dry, F A C P, Rochester, Minn, and Dr LeRoy H Sloan, F A C P, Chicago, Ill, were among those who conducted clinics John I Marker, F A C P, Colonel (MRC), U S Army, spoke on "The Medical Man and the Armed Services"

Under the Presidency of Dr Herbert Z Giffin, F A C P , Rochester, the Minnesota State Medical Association held its 89th Annual Meeting in Duluth, June 29 to July 1, 1942 Among the speakers at this meeting were

- Dr Archibald L Hoyne, F A C P , Chicago, Ill—"Modern Methods of Control for Measles, Scarlet Fever and Diphtheria",
 Dr Anton J Carlson, F A C P , Chicago, Ill—"Some Unknowns in the Pathologic Physiology of Aging"
 Dr Arthur C Christie, F A C P , Washington, D C , delivered the Russell D Carman Memorial Lecture on "Diagnosis and Treatment of Bronchiectasis," June 30

Dr Cyrus C Stungis, F A C P , Ann Arbor, Mich , spoke on "Coronary Thrombosis Discussion of Some of the Errors of Diagnosis," at the 64th Annual Meeting of the Medical Association of Montana, held in Missoula, July 8-10

Under the Presidency of Dr Carl Mulky, Albuquerque, the New Mexico Medical Society held its annual meeting in Santa Fe, June 25-27 Among the speakers were

- Dr Thomas D Cunningham, F A C P , Denver, Colo—"Allergy and Acute Disturbances of the Gastrointestinal Tract",
 Dr Franklin G Ebaugh, F A C P , Denver, Colo—"Prevalent Personality Problems of Childhood and Adolescence",
 Dr Meldrum K Wylder, F A C P , Albuquerque, N M—"Adequate Nutrition for Children During War Period"

Dr James W Vernon, F A C P , Moiganton, N C , has been chosen President-Elect of the Medical Society of the State of North Carolina

Dr Sidney F LeBauer, F A C P , Greensboro, spoke on "Rheumatic Fever, Diagnosis and Treatment," and Dr Tinsley R Harrison, F A C P , Winston-Salem, spoke on "The Nervous Heart," at a meeting of the Eighth District Medical Society in North Wilkesboro, N C , April 21

Dr Frederick R Taylor, F A C P , has been promoted to Associate Professor of Clinical Medicine at the Bowman Gray School of Medicine, Winston-Salem, N C

Dr Samuel R Kaufman, F A C P , Wilkes-Barre, Pa , spoke on "Allergy of the Eye, Ear, Nose and Throat," at the 1st Annual Meeting of the Eastern Pennsylvania Association of Eye, Ear, Nose and Throat Physicians, April 29, at the Schuylkill Country Club near Pottsville, Pa

Among the speakers at a meeting of the Wisconsin and Michigan Trudeau Societies held in Peltine, Wis , June 12-13, were

- Dr Christopher J Stringer (Associate), Lansing, Mich—"Sputum Examination Methods",
 Dr Anthony V Cadden, F A C P , Wauwatosa, Wis , and Dr David Salkin, F A C P , Hopewell, Va—"Preliminary Report on a Large Series of Routine Admission Bronchoscopies"

Dr William K Purks, F A C P, Vicksburg, Miss, spoke on "The Internist's Responsibility Regarding Surgical Problems of the Geriatric Patient," at the annual banquet of the Emory Medical Alumni Association, June 4, 1942

The Collegiate Division of the University of Chicago recently awarded an honorary citation to Dr Archibald L Hoyne, F A C P, Chicago, in special recognition of his achievements in the field of pediatrics

Dr Charles C De Gravelles, F A C P, New Iberia, has been chosen President-Elect of the Louisiana State Medical Society

The University of Michigan presented its Henry Russell Award to Dr Richard H Freyberg (Associate), Assistant Professor of Internal Medicine at the University of Michigan Medical School, for "distinguished achievement in medical research"

Dr Philip S Hench, F A C P, Rochester, Minn, was recently awarded the Heberden Medal for 1942 by the Heberden Society of London, "in recognition of his outstanding contributions to knowledge and progress in rheumatic diseases"

Dr Tom Bentley Throckmorton, F A C P, Des Moines, Iowa, spoke on "Psychotherapy in General Medicine and Surgery," at the National Assembly of the International College of Surgeons, held in Denver, Colo, July 15-18

Dr James O Ritchey, F A C P, Indianapolis, spoke on "Nontubercular Lesions of the Chest," at a meeting of the Eleventh Indiana Councilor District Medical Association in Flora, May 20

Dr Oscar W Bethea, F A C P, was recently chosen President-Elect of the New Orleans (La) Graduate Medical Assembly Dr Donovan C Browne, F A C P, is one of the Vice Presidents, Dr Joseph S D'Antoni (Associate), Secretary, and Dr William H Gillentine, F A C P, Treasurer

At a meeting of the Tenth District Medical Society of North Carolina in Asheville, May 27, the following members of the College spoke

Dr Wingate M Johnson, F A C P, Winston-Salem, N C—"The Nervous Patient",
Dr Charles H Armentrout (Associate), Asheville, N C—"Treatment of Congestive Heart Failure",

Dr Allison L Ormond (Associate), Black Mountain, N C—"Pleural Shock and Air Embolus in Artificial Pneumothorax"

Dr Thomas A Pitts, F A C P, Columbia, was installed as President of the South Carolina Medical Association at its recent meeting

At a symposium on "Coronary Occlusion" sponsored by the Salt Lake County (Utah) Medical Society Dr Fuller B Bailey, F A C P, spoke on "The Historical Background, Etiology and Diagnosis of Coronary Occlusion," and Dr Louis E Viko, F A C P, discussed "Diagnosis and Treatment of Coronary Occlusion"

Dr John W Preston, F A C P, Roanoke, and Dr Francis H Smith, F A C P, Abington, were recently re-appointed members of the State Board of Medical Examiners for a 4-year term by the Governor of Virginia

Dr George Blumer, F A C P, New Haven, Conn, was elected President of the Association of American Physicians at its annual meeting in Atlantic City, May 5-6, 1942. Among the other officers are Dr Warfield T Longcope, F A C P, Baltimore, Md, Vice President, and Dr Joseph T Wearn, F A C P, Cleveland, Ohio, Secretary.

Dr Joseph McFarland, F A C P, Emeritus Professor of Pathology at the University of Pennsylvania School of Medicine, Philadelphia, Pa, was given the 1941 Strittmatter Award of the Philadelphia County Medical Society on May 7, 1942. The award consists of a scroll, describing the accomplishments of the recipient, and a gold medal.

Among the members of the College with General Hospital No 17, Detroit, Mich, who were called to active duty with the Medical Corps of the U S Army, July 15, 1942, are the following:

Dr Henry R Carstens, F A C P, Colonel
 Dr Edward D Spalding, F A C P, Lieutenant Colonel
 Dr Douglas Donald, F A C P, Major
 Dr Charles Lemmon, F A C P, Major
 Dr Thomas N Horan, F A C P, Major
 Dr Frank S Perkin, F A C P, Major
 Dr Alvin E Price, F A C P, Major
 Dr Solomon Meyers, F A C P, Major
 Dr Abraham Becker (Associate), Captain

MISSING IN ACTION

The College has been notified that the following members are reported "missing in action" as of May 7, 1942:

James G Bruce (Associate), Captain (MRC), U S Army
 Robert Titus Phillips (Associate), Captain (MRC), U S Army

Captain Henry L Dollard, F A C P, Commanding Officer of the United States Naval Hospital in Philadelphia, was relieved of his duties there on July 6 for assignment elsewhere. Because of the high esteem and affection Captain and Mrs Dollard claimed from the medical profession and public of Philadelphia, a farewell dinner dance was tendered, at the Officers Club of the Philadelphia Navy Yard, in their honor on Friday evening, June 26. Among honored guests at the speakers table were Captain and Mrs R H Laning, Captain and Mrs W H H Turville, F A C P, Commander and Mrs C M Shaar, Commander and Mrs William L Martin, Commander and Mrs R T Canon, Lt Commander and Mrs Edward L Bortz, F A C P, Mr Edward R Loveland, Executive Secretary of the American College of Physicians, Dr Rufus S Reeves, F A C P, and Dr Louis H Clerf, F A C P.

Since Captain Dollard took command of the Naval Hospital at Philadelphia his friendly spirit and good will have fostered pleasant and congenial relations among the personnel of the hospital, the medical profession and the general public of the Fourth Naval District. He has frequently attended meetings of organized medicine in the district, and has likewise invited members of the profession to participate in scientific meetings at the Naval Hospital. It was with his cooperation and keen interest that the program of "Postgraduate Nights," an experiment in postgraduate education sponsored by the American College of Physicians during this past season

A graduate of Columbia, Captain Dollard has directed his untiring efforts and ambitions in the medical world to the service of the U S Navy. He has served at Naval Hospitals in New York, Newport, R I, San Diego, Calif, Chelsea, Mass, Great Lakes, Ill, and Charleston, S C, and he has carried the duties of Detail Officer at the Bureau of Medicine and Surgery in Washington. Likewise, he has served on many battleships and on foreign shore duty in the Philippines and in Samoa. For outstanding service Captain Dollard was awarded the Mexican Campaign medal, Haitian Campaign medal and the Victory medal. He has been a Fellow of the American College of Physicians since 1935.

Dr Roy L Leak, F A C P, Middletown, Conn, was elected President of the Connecticut State Medical Society at the Sesquicentennial Celebration of the State Society, which was held in Middletown on June 3 and 4, 1942. Dr Leak had been President-Elect during the years 1940-1941.

SPECIAL NOTICES

FEDERATION PROCEEDINGS

The Federation of American Societies for Experimental Biology, composed of The American Physiological Society, The American Society of Biological Chemists, The American Society for Pharmacology and Experimental Therapeutics, The American Society for Experimental Pathology, The American Institute of Nutrition and The American Association of Immunologists, has begun (1942) the publication of the Federation Proceedings.

Four issues will be published annually. Each year the *March* issue will contain the complete Federation Program of the scientific sessions of all the component Societies as prepared for the forthcoming annual meeting with abstracts of all scientific papers to be presented, the *June* and *September* issues will contain the full text of twenty or more papers presented at the annual meeting, including probably the papers on the joint society program and papers of several society symposia, the *December* issue will contain material pertinent to the Federation membership, i.e., the officers, membership list, together with an index of the completed volume.

The subscription price is \$4 (\$4.75 foreign) payable in advance. Subscriptions should be sent to Dr D R Hooker, Managing Editor, 19 West Chase Street, Baltimore, Maryland.

ANNOUNCEMENT OF FELLOWSHIPS IN MEDICINE AND PUBLIC HEALTH

The Commonwealth Fund of New York, a philanthropic foundation established in 1918 by the late Mrs Stephen V Harkness, announces that it is offering through the Pan American Sanitary Bureau fifteen fellowships for one year's study of public health subjects or postgraduate medical courses to properly qualified persons who are citizens of the other American republics. Fellowships in public health will be open to physicians, sanitary officers, technicians, public health nurses, etc. These fellows will be selected through a system of cooperation with medical and health authorities of the different countries concerned, and whenever deemed advisable they will be interviewed by traveling representatives of the Pan American Sanitary Bureau. Each fellowship will provide living allowances while the holder is in the United States, travel costs, and tuition. Knowledge of the English language will be among the requirements, and also the possession of certain specific qualifications.

The Pan American Sanitary Bureau, the international health agency of the American republics, has been for some time the recognized clearing house for

medical and public health fellowships in the United States, nearly 100 Latin Americans now being in the United States under its auspices

Application blanks giving complete information will be available through the Commonwealth Fund, 41 East 57th Street, New York, the Pan American Sanitary Bureau, Washington, D C , or chiefs of American Missions in Latin America

BINOCULARS FOR THE NAVY

The Fourth Naval District Public Relations Office, Philadelphia, Pa , has issued an appeal for the loan to the Navy of all binoculars having the specifications noted below There is a shortage of such instruments, and the antisubmarine patrols can be made more effective if the personnel are adequately equipped with such binoculars The Navy desires only instruments in good working condition, made by Bausch and Lomb, or by Zeiss, in sizes 6×30 or 7×50 —that is, with a magnification of 6 or 7 diameters and a front lens diameter of 30 or 50 millimeters Those with lower magnification or smaller aperture are not suitable and are not desired These two brands are specified because it is impracticable to keep in repair a heterogeneous lot of instruments If you have such an instrument and are willing to loan it to the Navy, you are requested to tag it with your name and send it to the Naval Observatory, Washington, D C

If you have such an instrument which needs minor repairs, or one which nearly meets these specifications, you are requested to write to the Naval Observatory, describing it and stating the size and name of manufacturer, and it will be called for if it can be used

As the Navy is not authorized to accept gifts or free loans, all binoculars accepted will be "purchased" for \$1 00 each If still in use at the end of the war, they will be returned to the owners and the \$1 00 will constitute a rental and depreciation fee

All binoculars accepted are engraved with the donor's name and a special serial number to identify them They are then issued immediately to naval vessels, and the commanding officers are requested to notify the donors of the name of the ships aboard which their binoculars are "serving in the navy"

OBITUARIES

DR JAMES D TRASK, 1942 PHILLIPS' MEDALIST OF THE A C P DIES

Dr James Dowling Trask, who, with Dr John R Paul, was the recipient of the 1942 Phillips Award of the American College of Physicians, died suddenly in Chicago, May 24, 1942 Dr Trask was Associate Professor of Pediatrics at Yale University School of Medicine Dr Trask had a brilliant research record in the field of poliomyelitis His studies in the clinical epidemiology of this disease have brought us much nearer the truth Control is more nearly a reality because of the contributions of Dr Trask and Dr Paul.

DR HOWARD LEON JAMESON

The American College of Physicians has lost a loyal friend and member with the passing of Dr Howard L Jameson, who died on July 1, 1942 in the Graduate Hospital after a short illness

Dr Jameson was born in New Jersey on September 6, 1881. His earlier education was received at the New Egypt public schools and the New Egypt Seminary and Female College. In 1906 he received his Medical Doctor's Degree from the Medico-Chirurgical College of Philadelphia.

Shortly after receiving his degree, Dr Jameson became an instructor and lecturer in medicine at the Medico-Chirurgical College, and Assistant Physician to the Medico-Chirurgical Hospital and the Polyclinic Hospital. With the combination of these two centers and the inception of the Graduate School of Medicine of the University of Pennsylvania, Dr Jameson continued his career as a teacher. He served as Assistant Professor of Medicine, Associate Professor of Medicine and, at the time of his death, was Professor of Clinical Medicine, University of Pennsylvania Graduate School of Medicine and Graduate Hospital of the University of Pennsylvania.

His identification with organized medicine included membership in the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, the Philadelphia Pediatric Society, the Medical Club of Philadelphia. He was likewise a member of the American Therapeutic Society, the Aesculapian Club of Philadelphia, the American Medical Association, and, since 1926, Dr Jameson had been a Fellow of The American College of Physicians. He was also a Diplomate of the American Board of Internal Medicine.

Long an active and interested member in the activities of his profession, the death of Dr Jameson will cause deep sorrow to his many friends.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR EDWIN A. BAUMGARTNER

Dr Edwin A. Baumgartner, a Fellow since 1926, died on March 15, 1942, of rheumatoid arthritis. For the last twenty-two years of his life he suffered almost constant pain but he had the courage to rise above a condition which would have made most people accept invalidism.

Dr Baumgartner was born February 14, 1888, at Halstead, Kansas, and received his A.B. degree from the University of Kansas in 1910. His early training was in anatomy, and in 1911 he received his M.A. from the University of Kansas, in 1915 his Ph.D. from the University of Minnesota, and in 1919 his M.D. from Washington University School of Medicine in St. Louis. During these years he was an instructor in Anatomy, from 1911-1912 in the University of Wisconsin, and from 1912-1914 at the University of Minnesota. From 1914-1919 he was Associate in Anatomy at Washington University School of Medicine and during these years he published six papers on anatomical subjects. During the years 1918-1920 he also served as intern in Barnes Hospital and intern in Pathology at the Halstead Hospital under Dr. A. E. Hertzler. He then determined to become a surgeon and was surgical assistant to Dr. H. Mudd in St. Louis, 1920-1921, but

during this period he had his first attack of rheumatoid arthritis, which left him so crippled that further surgery was out of the question. He then turned his attention to pathology and during the years 1921-1932 he was the Associate Pathologist at the Clifton Springs Sanitarium, during which time his name was associated with forty-eight papers of clinico-pathological interest and a wide variety of subjects. In December 1932 he was appointed Pathologist at the Newark State School and County Laboratory at Newark, N. Y. During this period his name was associated with five publications. He was an indefatigable worker and in addition to being a thorough scientist, was a good teacher and an inspiration to the men with whom he came in contact. Only his close associates realized the handicaps under which he worked.

SAMUEL A. MUNFORD, M.D. (Associate)

DR. MANSON MICHAEL LAIRY

Dr. Manson Michael Lairy, F.A.C.P., La Fayette, Indiana, died April 13, 1942, of mesenteric embolus and auricular fibrillation, aged 80 years.

Dr. Lairy was born in La Fayette, Ind., in 1862. He attended the Indiana University School of Medicine, receiving his medical degree in 1893. Later he did postgraduate work at the New York Post-Graduate Medical School and Hospital. For many years he was a member of the staff of St. Elizabeth and La Fayette Home Hospitals, and Medical Chief of St. Joseph's Orphanage. He was formerly Medical Director of the La Fayette Life Insurance Company and he had served at one time as a member of the La Fayette City Council and also as a member of the La Fayette Board of Education. He retired from active practice in 1939.

Dr. Lairy was a former President of the Tippecanoe County Medical Society, a member of the Indiana State Medical Society, a Fellow of the American Medical Association, and had been a Fellow of The American College of Physicians since 1922.

DR. JACOB GREKIN

Dr. Jacob Grekin (Associate) of Pittsburgh died April 5, 1942, of coronary thrombosis, aged 62. He was born in Russia in 1880, graduated from the Gymnasium, Odessa, 1897, his pre-medical and medical training were received at the University of Pittsburgh School of Medicine, from which he graduated in 1908, in 1926-27 he did postgraduate study at the University of Vienna. For many years he was Chief of the Department of Pathology at Montefiore Hospital, Pittsburgh, and since 1926 had been Chief in Medicine at that institution. Dr. Grekin was a member of his county and state medical societies, a Fellow of the American Medical Association, and since 1926 had been an Associate of the American College of Physicians.

It was the privilege of the undersigned to know Dr Grekin since his senior year in the medical department of the University of Pittsburgh. Through all this period he was a most earnest student and conscientious practitioner. While keeping thoroughly abreast of medical literature, he was also well informed in the arts, particularly music. There was almost nothing in symphonic or operatic scores with which he was not familiar.

World events were likewise closely followed and even with the kaleidoscopic conditions of the past few years, he always seemed to have a bird's-eye view of the whole.

By his medical confreres he was regarded with the greatest respect, both for his ability and his integrity. He will be greatly missed by them, by his patients and by a large circle of friends.

MILTON GOLDSMITH, M D , F A C P

DR JESSE LUTHER LENKER

Pennsylvania Medicine suffered the loss of a true friend with the passing of Dr Jesse Luther Lenker of Harrisburg, Pa., on June 2, 1942.

Dr Lenker was born September 30, 1882, in Harrisburg. The greater part of his boyhood was spent in and about Linglestown, Pa., where he attended the public schools. He attended Millersville State Teachers College, and upon graduation taught school for two years. He then entered the Baltimore Medical College, now a part of the University of Maryland, and received his M D degree in 1907. He served a junior internship during the summer of 1906 at the Harrisburg Hospital, and his regular internship through 1907-08 at the same institution. He began practicing medicine in Harrisburg in 1908. After that time he did graduate study at the Harvard Medical School, including the Massachusetts General Hospital and the Peter Bent Brigham Hospital, and attended numerous clinics in this country and in Europe. Gettysburg College conferred upon him the honorary degree of Doctor of Science in 1931.

From 1908 Dr Lenker was associated with the Harrisburg Hospital, serving as assistant anesthetist, anesthetist, dispensary physician, visiting physician, instructor in medicine, cardiologist, medical director and dean of staff. At the time of his death he was also chief of the visiting staff of the Convalescent Home, operated by the Junior League, and consulting physician for the Harrisburg Draft Boards. An active participant in the labors of organized medicine, Dr Lenker served as President and also Secretary of the Dauphin County Medical Society, Secretary-Treasurer and also President of the Harrisburg Academy of Medicine, Secretary and also Chairman of the Medical Section of the Medical Society of the State of Pennsylvania. In addition to the duties imposed upon him in these various offices, he found time to add, in no small measure, to the field of medical literature, being the author of many published papers.

Dr Lenker was a member of the Philadelphia Medical Club, the American Heart Society, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1927. He served on the Governor's Committee for Eastern Pennsylvania and was a guiding spirit in the affairs of the American College of Physicians. He died at his office on June 2 of a cerebral hemorrhage, after having had an earlier attack on December 28, 1941, from which he had apparently fairly well recovered. With his death the College lost one of its outstanding members.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. HENRY WALLACE GROTE

Dr. Henry Wallace Grote of Bloomington, Illinois, Associate of the American College of Physicians since 1925, died at his home, 1502 East Grove Street, Saturday, June 19, 1942, of carcinoma of the prostate.

Dr. Grote was born in Wheaton, Illinois, July 11, 1869. He attended and graduated from the Wheaton schools and from Wheaton College in 1888. In 1891 he graduated from the Illinois College of Pharmacy with a Ph.G. degree.

He matriculated at Rush Medical College, graduating with an M.D. degree in 1894, and continued study as a post-graduate at the New York Polyclinic Medical School in 1896 and 1897.

In Bloomington, Dr. Grote had a notable career. For many years he was roentgenologist at St. Joseph Hospital, Bloomington, Illinois, and at Brokaw Hospital, Normal, Illinois.

He was active in medical groups, holding membership in the McLean County Medical Society, of which he was at one time president, the Illinois State Medical Society, the American Roentgen Ray Society, Radiological Society of North America, American College of Physical Therapy, former president of the Central Illinois Radiological Society, Associate of the American College of Physicians since 1925.

His life, which was full and varied, was devoted to the service of others. His pleasing personality and keen sense of humor were admired and liked by professional colleagues and friends. It is with a deep sense of loss that we write of his passing.

E. M. STEVENSON, M.D., F.A.C.P.,
Bloomington, Ill.

MINUTES OF THE BOARD OF REGENTS

ST PAUL, MINN

APRIL 21, 1942

The second meeting of the Board of Regents in conjunction with the Twenty-sixth Annual Session of the American College of Physicians convened in the Municipal Auditorium, St Paul, Minn, Tuesday at 12 00 Noon, President Roger I Lee, of Boston, Mass, presiding and Mr E R Loveland acting as Secretary, with the following members in attendance

Roger I Lee	<i>President</i>
James E Paullin	<i>President-Elect</i>
Thomas T Holt	<i>Second Vice-President</i>
Samuel E Munson	<i>Third Vice-President</i>
William D Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary-General</i>
Reginald Fitz	
William J Kerr	
Charles T Stone	
J Morrison Hutcheson	
T Homer Coffen	
Ernest E Irons	
Jonathan C Meakins	
Charles H Cocke	

The Secretary read abstracted minutes of the preceding meeting, April 19, 1942, which were approved as read

PRESIDENT ROGER I LEE Would the Chairman of the Board of Governors care to make a report at this time?

DR CHARLES H COCKE, CHAIRMAN I had an interesting discussion yesterday of the present situation as it relates to men in service or about to be inducted There is considerable concern about Associates in service whose time is approaching the end of the five-year period, during which they must qualify for Fellowship or be dropped Naturally, if they are in service it is quite problematic whether they will be given an opportunity to fulfill the necessary requirements during the time of military service

The matter has also come up concerning Governors who are on active duty This situation has already occurred in the case of the Governor for Maine and the Governor for Eastern Pennsylvania The only possible entry into this organization is through proposals which must be endorsed by the local Governor, and if he is away on military service, such proposals cannot be completed

As a result of this discussion the following resolution was passed by the Board of Governors, the motion being made by Dr T Z Cason, Governor for Florida and regularly seconded by Dr Alex M Burgess, Governor for Rhode Island, that the Board of Governors go on record as requesting no change be made that would not otherwise be made in the status of the men, either in the service or contemplating early entry, and wherever it is requested by the Governor of a state that an Acting Governor be appointed until his return, that the Board of Regents be requested to adopt a resolution authorizing an Acting Governor in this emergency

There should be a continuity of action on the part of the Governors who may be called into service I move that the Regents make some such provision

PRESIDENT LEE Is that strictly legal under our By-Laws?

DR T HOMER COFFEN Mr President, Article IV says that the President shall fill all vacancies on the Board of Governors, but I suppose the Acting Governor could be nominated by the Governor of the state

DR COCKE The Governor would not like to give up his position because he does not know what his term of service may be

SECRETARY LOVELAND I believe the proposed action is within provisions of the By-Laws However, there should be some control over the appointment of the Acting Governor I think his appointment should be subject to the approval of some designated committee, such as the Executive Committee, or the President By acceptance of this resolution you are putting the matter wholly in the Governor's hands, and if he should not choose to appoint an Acting Governor there would be another situation Possibly the resolution should provide that whenever, in the judgment of the Executive Committee, any particular Governor cannot function because of military service, an Acting Governor may be appointed and that Acting Governor shall be approved by the Executive Committee or the President Perhaps the Chairman of the Board of Governors has some suggestion

DR COCKE The resolution states that "an Acting Governor be appointed until his return" It does not say that he shall be appointed by the Governor of the state I think Mr Loveland's point is quite proper The Governor on duty might be asked to submit the names of one, two or more men, as the Executive Committee may desire, and then the appointment should reside in the hands of the President or the Executive Committee

I move that the Board of Regents activate this suggestion and this resolution

PRESIDENT LEE I will entertain a motion moved by Dr Cocke, that the report of the Governors be accepted by the Regents If that report is accepted we can take action subsequently

Dr William D Stroud seconded the motion and it was regularly carried

PRESIDENT LEE Now a motion will be in order as to how to activate this resolution

DR JONATHAN C MEAKINS I move, Mr President, that the Executive Committee be empowered to appoint an Acting, or interim, Governor on notification of the Governor that he is going into active service

DR COCKE I second the motion

PRESIDENT LEE During the emergency the Executive Committee on notification from a Governor that he is called to active service and will probably be unable to serve sufficiently as Governor is empowered to designate an Acting Governor

DR GEORGE MORRIS PIERSON The mere fact he is being called to active service may not interfere with his functioning The provision should be, "if he is called and finds himself unable to serve sufficiently"

DR MEAKINS Do you not think each Governor should be formally informed of this? The Executive Secretary should write to each Governor drawing his attention to this A mere report to the Board of Governors at its meeting might not be effective because some members would be absent and others might forget

PRESIDENT LEE It is understood that the Executive Committee has the authority, in the case of the inability of a Governor to perform his duties because of going into active service, to designate an Acting Governor Let it be thoroughly publicized

Those in favor say "Aye", opposed, "No"

The motion was carried

DR COCKE Action should be taken on the other matter, namely, the extension of the maximum five-year Associateship term in the case of Associates who are on active duty and who may be prevented thereby from qualifying for advancement to Fellowship Such men should not be penalized for patriotic duty

PRESIDENT LEE The Chair would prefer to refer this matter to the Committee on Credentials and wait for a report later Is that agreeable, Dr Cocke?

DR COCKE Quite agreeable

The meeting adjourned at 1 00 p m for luncheon

RECESS

The meeting was called to order at 1 30 p m by President Lee

DR COCKE The Committee on Credentials will meet at the conclusion of this meeting for consideration of specific recommendations in regard to the extension of the Associateship term in the case of men in active military service

PRESIDENT LEE The particular and pressing matter which I think ought to be discussed today and possibly decided upon is the question of future policy with regard to fees and dues of members in the armed forces That has come before two committees, the Committee on Finance which has factual evidence to present but which does not care to recommend a policy, and the Committee on Public Relations

DR JAMES E PAULLIN Would you care to have the Committee on Finance report their estimates on the financial change there would be under certain circumstances of reducing dues, and as to whether the College can afford it? Dr Stone is the Acting Chairman of the Finance Committee

PRESIDENT LEE I will call for that portion of the report which deals with that item

DR CHARLES T STONE I have conferred freely with the President, with the former Chairman of the Finance Committee, with the Executive Secretary and have had the benefit of advice and counsel from the Treasurer We have drawn up some recommendations for your consideration The Committee has for its guidance a letter from Dr Perry Pepper, the Chairman, and his recommendations have been largely included in the recommendation which we feel disposed to make

Reading from the fifth paragraph of the report of the Committee on Finance

"The Committee on Finance has carefully considered the financial status of the College and finds that there will be an estimated net income of about \$30,000 for 1942 It is recommended, therefore, that the Board of Regents waive the dues of all members, Associates and Fellows, who are called to active duty with the armed forces, and that the Initiation Fee for Fellows on active duty be reduced from \$80 00 to \$10 00, both effective January 1, 1942"

The Committee believes that the College would lose about \$5,000 annually by the adoption of this recommendation Therefore, by the adoption of this recommendation the College would automatically decrease its income per annum approximately \$5,000

PRESIDENT LEE I now call upon the Chairman of the Committee on Public Relations, Dr Paullin

DR PAULLIN Mr President, after receipt of the recommendation of the Committee on Finance, the Committee on Public Relations presents the recommendation that the following resolution be adopted

'BE IT RESOLVED, in view of the present emergency, all members Associates and Fellows, of the American College of Physicians who are called to active military duty with the armed forces be accorded waiver of dues during their period of active service and complete detachment from private practice, such waiver to be operative from January 1, 1942

'Such members shall inform the Executive Secretary of the date of entrance upon military duty and of the date of discharge therefrom

"In view of the necessary changing locations of these members and the inherent difficulty of supplying the ANNALS OF INTERNAL MEDICINE, the journal and other publications shall not be furnished

"BE IT FURTHER RESOLVED the Initiation Fee of members serving with the armed forces be reduced to ten dollars"

PRESIDENT LEE We will open this matter for discussion. It is pointed out that the College of Surgeons attempts to collect \$500 from each Fellow, and that waiver of dues does not mitigate this \$500. I think I am right. The Canadian Medical Association has remitted the dues of its members on active service. It does not give these members the journal. The Chair has taken unto itself the liberty, which it shouldn't do, of discussing this matter. It is possible for any one of our members to come before the College for a reduction of dues, giving specific instances. The present provision for reduction of dues does not apply to men not wholly detached from private practice. The proposed resolution likewise does not include men not wholly detached from private practice. We want this to be understood. There would be, perhaps, members who would be aggrieved. Some members in Boston, Philadelphia and a number of places where they have Naval Hospitals might be in naval practice certain parts of the day, with the rest of the time to carry on private practice.

DR STROUD Mr President, as Treasurer I think the Board should understand the situation at present to a certain degree. We are in a very sound financial condition. The Executive Secretary's estimated income and expenses always seem to be fulfilled. He estimated that we should have a surplus of income over expenses for 1942 of between \$28,000 and \$30,000. We have in cash in the General Fund \$78,000, of which the Finance Committee is suggesting investment of \$28,000, so that we shall have \$50,000 in cash in the General Fund for emergencies. Now if the proposed resolution would result in a reduction in income, even of \$6,000 or \$7,000, I personally feel that the action is justified, and that the College should take this reduction.

The second point I should like to raise is that of sending the ANNALS. If any of the members wish to subscribe for the ANNALS in the usual way while on active duty, they could pay for it.

SECRETARY LOVELAND The adoption of this resolution would mean that we should refund, pro rata, dues that have been paid since January 1, 1942?

DR PAULLIN Yes.

SECRETARY LOVELAND The majority of members have already paid their 1942 dues.

DR STROUD Mr Loveland, your point is, I believe, that it would not be fair to put this motion through and have those who have already paid their dues lose out because they have been honest and prompt.

SECRETARY LOVELAND The provision must be made retroactive to January 1 so that all members shall be treated alike.

DR STONE Mr Loveland has just handed me, since I made my original remarks, a revision of the total amount that the College would lose by waiving the dues and reducing the Initiation Fee, namely, \$6,000 annually instead of \$5,000.

PRESIDENT LEE Dr Paullin do you want to amend the resolution to date from January 1, 1943?

DR PAULLIN No. January 1, 1942.

PRESIDENT LEE And have a refund?

DR PAULLIN Yes.

DR PIERSON How does that affect the men who are regular officers in the Army and Navy?

SECRETARY LOVELAND We should have to refund to everybody, alike.

DR PIERSON Even those men whose life work is in the Army and Navy, during this emergency would their dues be waived, or if paid, refunded?

SECRETARY LOVELAND That is the intent of this motion.

PRESIDENT LEE It should be stated furthermore that this does not include the U. S. Public Health Service and other Government officials, Red Cross, et cetera.

DR PAULLIN Nor does it include the Veterans Administration or Civil Service

DR KERR Mr President, would it not be a generous thing on our part, if through the Surgeons General we might provide a certain number of subscriptions to the ANNALS OF INTERNAL MEDICINE to be distributed to their hospitals for the benefit of the men in service, as a contribution from the College?

PRESIDENT LEE The Surgeons General's offices subscribe to a certain number of medical journals. We have been trying to get them to stock their libraries with appropriate medical journals and books. They have adequate funds.

Is there any further discussion? I think this is as vital a matter as has come up at this Session.

DR COCKE Mr President, I move the adoption of these resolutions.

DR PIERSOL I second that motion.

The question was called and the motion carried.

PRESIDENT LEE May we now consider the question of reduction in the fees in connection with the American Board of Internal Medicine? Has the Finance Committee any recommendations?

DR STONE Item No 7 on the Finance Report states

"The Committee on Finance has learned that certain regional opinion is favorable to a reduction in the Initiation Fee of the College. The Committee feels that the financial condition of the College is such that it could safely stand a reduction of the Initiation Fee, up to twenty per cent, but it transmits this information to the Board of Regents without recommendation."

PRESIDENT LEE What difference would that make in the income of the College?

DR STONE The Executive Secretary has estimated that the reduction in Initiation Fees by twenty per cent, comparable to that which has been suggested by the American Board of Internal Medicine, would reduce the income \$4,000 annually.

DR PAULLIN The present Initiation Fee for practicing physicians is \$80 00?

SECRETARY LOVELAND Yes, a twenty per cent reduction would make the fee approximately \$65 00.

DR PAULLIN What is the fee for the American Board?

DR STONE \$50 00, the Board is willing to reduce it twenty per cent, to \$40 00.

PRESIDENT LEE The matter for consideration before this house is that in co-operation with the American Board of Internal Medicine, which contemplates the reduction in its fees from \$50 00 to \$40 00, this College reduce its Initiation Fee from \$80 00 to \$65 00. This reduces the total cost to a physician for certification and Fellowship in the College from \$130 00 to \$105 00. I take it the American Board of Internal Medicine would like to have a joint action on the part of the College and their Board, and I also understand that action would not become operative until January 1, 1943.

DR IRONS The American Board of Internal Medicine wishes to cooperate with the College. We cannot act in conjunction with the College because we are entirely separate.

DR COCKE I move the adoption of the following resolution.

RESOLVED That in consideration of action contemplated by the American Board of Internal Medicine to reduce their total certification fee from \$50 00 to \$40 00, the American College of Physicians shall reduce its Initiation Fee for practicing clinicians from \$80 00 to \$65 00, this action to become effective January 1, 1943, and to be dependent upon consummation of similar action by the American Board of Internal Medicine.

DR STONE I second the motion.

There was no further discussion, question was called, and the motion carried

PRESIDENT LEE We will call upon the Chairman of the Committee on Public Relations for the balance of his report

DR PAULLIN This Committee recommends that the following delinquent members of two or more years' standing be dropped from the Roster in accordance with provisions of the By-Laws. They have tendered resignations, but they are not eligible to resign because they are delinquent

DR STROUD I second the motion

There was no discussion, question was called, and the motion was carried

DR PAULLIN The Committee recommends that the resignations of the following 7 Associates and 3 Fellows, in good standing, be accepted

Marshall S. Brown, Jr (Associate), New York, N. Y.

Ray S. Dixon (Associate), Detroit, Mich.

Philip J. Lukens (Associate), Ambler, Pa.

Bernard T. McGhie (Fellow), Toronto, Ont.

E. C. Rinehart (Associate), Struthers, Ohio

John R. Rodger (Associate), Bellane, Mich.

F. M. Routh (Associate), Columbia, S. C.

Richard Harry Schmitt (Associate), Buffalo, N. Y.

G. Louis Weller, Jr (Fellow), Washington, D. C.

Pauline Williams (Fellow), Richmond, Va.

On motion by Dr. Paullin, seconded by Dr. Keir and regularly carried these resignations were accepted

DR PAULLIN The following 2 Associates and 2 Fellows are delinquent in dues for two or more years and subject to being dropped automatically. Numerous letters have been addressed to them

It is recommended that these names be discontinued in accordance with the By-Laws

Dr. _____, Fellow, is also delinquent, and in addition, the College is unable to locate his whereabouts after several months of effort. It is recommended that he also be dropped

Dr. _____, Associate, was totally disabled and out of practice from February, 1939, until July, 1941. He had very little income, and since he showed exceedingly good faith in paying the minimum dues for 1940 and 1941, it is suggested by the Executive Secretary and recommended by this Committee that his dues be waived for those years, and that the amount which he has paid be applied to his account of 1942 dues. He has been sick and unable to pay.

I move the above recommendations be accepted

DR STONE I second the motion

The question was called and the motion was carried

DR PAULLIN Another Fellow, Dr. _____, is delinquent for 1940 and 1941. During this time he was on military duty in England, and in view of a similar courtesy extended by the Canadian Medical Association he feels that the American College of Physicians should waive his dues for those years, and he, in turn, will pay full dues for 1942. This case brings up a question of policy concerning waiver of dues in full rather than reduction in cases of military service. The new regulation adopted by this Board covers the period from January 1, 1942, but this case precedes that time. Your Committee recommends his dues be waived for 1940 and 1941 in

keeping with the resolution which has been previously passed, permitting men in military service to apply for such waiver I so move

DR PIERSON I second the motion

There was no further discussion, question was called and the motion carried

I move that the report of the Committee on Public Relations as a whole be accepted

The motion was seconded and regularly carried

PRESIDENT LEE May we have the balance of the report of the Finance Committee, Dr Stone?

DR STONE The remainder of my report has to do more or less with routine matters

I 'The Committee on Finance has examined the auditor's report and the financial statements of the College for 1941 and recommends the receipt and approval of these reports by the Board of Regents, in accordance with copies already placed in your hands "

It is so moved by the Committee

DR PAULLIN I second the motion

The question was called and the motion carried

DR STONE The Committee moved the adoption of the following resolution

II 'RESOLVED That the suggestions of our Investment Council that our holdings in Florida Power Corporation, the Michigan Consolidated Gas Company and the Virginia Public Service Company be sold and that the proceeds derived therefrom be used to purchase \$10,000 United States of America 2½% notes, 1952-55, at market, one Florida Power and Light Company bond, and fifty shares of the United Gas Improvement Company preferred stock "

This transaction will leave approximately \$14,000 in cash in the Endowment Fund and \$78,000 in cash in the General Fund

DR COFFEN I second the motion

PRESIDENT LEE Are we voting to accept the recommendation of the Investment Council that certain securities be sold and certain others as mentioned be purchased? The Chair has a rather definite idea about this It is up to the Finance Committee to change its own stock and that ought not to be voted by the Board of Regents The Board of Regents can approve in general, but it has been discussed before and would seem unfortunate to have the Board of Regents involved in details for the sale of stock, and so the Chair would entertain a motion that the Board of Regents approve this paragraph

DR STONE I so move

DR PAULLIN I second the motion

The question was called and the motion carried

DR STONE The Finance Committee reports its adoption of the following resolution

III 'RESOLVED That \$14,000 uninvested principal in the Endowment Fund be used to purchase interest bearing United States War Bonds, subject to the approval of our Investment Council "

PRESIDENT LEE All those in favor of accepting this part of the report as contemplated action say 'Aye", opposed 'No "

The Board was unanimously in favor of accepting the report

DR STONE The Finance Committee reports the following resolution as contemplated action

IV "RESOLVED That the recommendation by our Investment Council that we invest approximately \$28,000 uninvested cash in the General Fund be approved"

On motion made, seconded and regularly carried this contemplated action was approved

DR STONE The only other matter to be brought before this meeting is that which has to do with the handling of securities by the Investment Council, Drexel and Company, of Philadelphia

It is recommended that the Board of Regents approve of the following official resolutions to facilitate the handling of securities, and I move their acceptance

"RESOLVED That the Treasurer or the Chairman of the Finance Committee be and is hereby authorized to deliver any and all securities, standing in the name of or belonging to the American College of Physicians, to Drexel & Co for the purpose of opening a Custody Account in the name of the American College of Physicians

"FURTHER RESOLVED That Drexel & Co be and is hereby authorized to register any and all securities so delivered in the name of their nominee or nominees for the purpose of facilitating brokerage transactions made for the Account of the American College of Physicians and for the purpose of collecting dividends and interest on securities so registered, and to detach any and all interest or dividend coupons from unregistered securities as and when they shall become due and payable

"FURTHER RESOLVED That Drexel & Co be and is hereby authorized to collect the principal on any and all securities when it shall become due and payable

"FURTHER RESOLVED That Drexel & Co be and is hereby authorized to hold any and all monies so collected for the Account of the American College of Physicians, and to remit any and all monies to the American College of Physicians in any manner so directed upon the written instructions of the Treasurer or the Chairman of the Finance Committee

"FURTHER RESOLVED That Drexel & Co be and is hereby authorized to sell, assign, transfer or deliver any and all securities deposited in the aforesaid Custody Account, and to purchase additional securities for the Account of the American College of Physicians, upon the written instructions of the Treasurer or the Chairman of the Finance Committee

I hereby certify that the following named persons have been duly elected and now hold the offices above referred to, namely,

Treasurer
Chairman, Finance Committee
Executive Secretary "

DR MEAKINS. I second the motion

There was no discussion the question was called and the motion carried

DR STONE I move that the report as a whole be accepted

DR MEAKINS I second it

The question was called and the motion carried

PRESIDENT LEE We will now have the report of the Treasurer

DR STROUD The financial reports * have just been placed in your hands, and I

* These reports appear at the end of these Minutes

think they explain themselves Our finances are in excellent shape Our Investment Council has been doing very satisfactory work, and we have continued confidence in him

On motion made, seconded and regularly carried, the report of the Treasurer, along with the financial reports, hereto appended, was accepted with grateful thanks

PRESIDENT LEE Have you any business, Dr Irons, concerning the division of Illinois in regard to Governors' territories?

DR IRONS This matter is carried over from the last meeting of this Board The purpose is to settle a difficulty which has existed for some time between the division of Illinois territory for the Northern and Southern sections Many years ago a line was drawn through the center of the state The Governor of Southern Illinois found objection because there were so few towns and consequently few internists in his half of the state Consequently, an agreement between the two Governors has been sought Now I have a letter from the two Governors showing that they have reached an equitable agreement I will read the letter

"April 20, 1942

The Board of Regents
American College of Physicians
Gentlemen

After due consideration we respectfully recommend to the Board of Regents that the dividing line between Northern and Southern districts of the State of Illinois be established at the 41st (forty-first) parallel, as per the accompanying map

Very truly,

(Signed) C M Jack
Governor for Southern Illinois
(Signed) LeRoy Sloan
Governor for Northern Illinois"

I move the approval of the recommendation of the Governors

DR STONE I second it

PRESIDENT LEE I recognize Dr Munson

DR MUNSON Because of my association for the last fifteen or twenty years with the Illinois State Medical Society, I have known the physicians over the state, outside of Chicago, better, perhaps, than the Governor of Northern Illinois himself Originally I was the College Governor for Illinois as a whole, and the men responded to my call for regional meetings generally over the state It was impracticable, however, for me to continue serving the entire state because I did not know the physicians so well in Chicago, and, therefore, the state was divided The 41st parallel is just north of Peoria The division is perfectly satisfactory to me

PRESIDENT LEE I understand this recommendation is satisfactory to both Governors, to the Executive Offices, and I see no reason for further delay

PRESIDENT LEE Is there any further discussion? If not, all in favor say "Aye", opposed "No"

The motion was carried

PRESIDENT LEE Is there any further business that should come before the House?

DR COFFEN Mr President, there is one matter I would like to speak of in the absence of Dr Edward L Bortz, particularly in regard to Postgraduate Nights, that have been so successfully held in some military stations and sponsored by the College The thought is that they ought to be extended to various parts of the country I can see how well would be received such a program, presented by members of the College, in various locations I do not know that we need any action on it, except that

the Regents might go on record as endorsing or encouraging Dr Bortz and the Advisory Committee on Postgraduate Courses that arranges for such courses

PRESIDENT LEE Do you make that in the form of a motion?

DR COFFEN I do

DR PIERSOL I second the motion

DR MUNSON Will these meetings be held annually?

DR COFFEN No, at any time during the year

PRESIDENT LEE I take it this will be extended to Government Camps, General Hospitals and large Station Hospitals, et cetera I may say that the Surgeon General is very much in favor of that extension and development whenever and wherever military exigencies permit All in favor of the motion say "Aye", opposed "No"

The motion was carried

President Lee made numerous announcements concerning forthcoming functions and meetings and thereafter the meeting adjourned at 2 15 p m

Attest (Signed) E R LOVELAND,

Secretary

GENERAL FUND

For the Year Ended December 31, 1941

Balance, January 1, 1941		\$146,922 48
Add Dividend received from Bank of Pittsburgh, National Association, in excess of deposit		753 21
		<hr/>
		\$147,675 69
Less		
Transfer to Endowment Fund of the Initiation Fees of Life Members	\$ 1,374 53	
To close Deferred Claim against Exchange National Bank, Pittsburgh	111 95	
Adjustment of Furniture and Equipment Account	88 00	1,574 48
	<hr/>	<hr/>
		\$146,101 21

Summary of Operations for the Year ended December 31, 1941

Income

Annual Dues	\$30,725 19	
Initiation Fees	20,702 00	
Subscriptions, ANNALS OF INTERNAL MEDICINE	30,943 69	
Advertising, ANNALS OF INTERNAL MEDICINE	9,096 12	
Income from Invested Funds, General	4,279 16	
Income from Invested Funds, Endowment	4,483 79	
Exhibits, 25th Annual Session	11,474 14	
Guest Fees, 25th Annual Session and Banquet, net	696 70	
Profit on Keys, Pledges and Frames	154 29	
Dividend on Perpetual Insurance Deposit	60 00	
Postgraduate Courses, net	127 25	
Sale of Directory, 1939 and 1941	99 75	
	<hr/>	
TOTAL INCOME		\$112,842 08

Expenses

Salaries	\$26,044 70	
Postage, Telephone and Telegraph	4,001 11	
Office Supplies and Stationery	1,120 27	
Printing	24,616 21	
Traveling Expenses	4,115 12	
College Headquarters		
Maintenance	\$2,102 59	
Heat, Light, Gas and Water	673 31	
Taxes	1,239 22	
Insurance	236 85	4,251 97
	<hr/>	
Depreciation on Building, Furniture and Equipment	1,857 98	
Grant to National Research Council	7,500 00	
1941 Directory	3,075 78	
John Phillips Memorial Prize	12 31	
Research Fellowships	5,708 64	
Loss on Sale or Maturity of Investments	1,312 40	
Regional Meetings	368 21	
College History	1,861 23	
Investment, Real Estate, net	369 78	
Other Expenses		
25th Annual Session	\$1,911 96	
ANNALS OF INTERNAL MEDICINE	587 48	
Miscellaneous	874 57	6 375 91
	<hr/>	<hr/>
TOTAL EXPENSES		\$ 92,619 65
Net Income for the Year Ended December 31, 1941		20,222 40
Balance December 31, 1941		<hr/>
		\$166,325 61



ENDOWMENT FUND

For the Year Ended December 31, 1941

Principal Account, January 1, 1941		\$126,346 22
Add		
Life Membership Fees received during 1941	\$4,235 47	
Transfer of Initiation Fees of New Life Members from General Fund	1,374 53	
Gain on Investment Transactions, net of Losses	630 16	
Total Increase during 1941		6,240 16
Principal Account, December 31, 1941		<u>\$132,586 38</u>
Income Account		
Income from Investments earned during 1941		\$ 4,483 79
Deduct		
Research Fellowships	\$5,708 64	
John Phillips Memorial Prize	42 34	5,750 98
Excess of Expenses over Income, charged to General Fund Operations for 1941		<u>\$ 1,267 19</u>

INVESTMENTS

December 31, 1941

<i>Par Value</i>	<i>Bonds</i>	<i>Endowment Fund Investments</i>	<i>General Fund Investments</i>
\$ 5,000	Carolina Clinchfield & Ohio Ry , 1st Mort , Series "A," 4s, 1965	\$ 5,125 00	
10,000	Federal Farm Mortgage Corp , 3s, 1944-49		\$10,875 00
5,000	Florida Power Corp , 1st Mort , Series "C," 4s, 1966	4,485 90	
4,000	Florida Power & Light, 1st Mort , 5s, 1954	4,226 25	
5,000	Great Northern Railway, Gen Mort , Series "B," 5½s, 1952	4,463 45	
5,000	Michigan Consolidated Gas, 1st Mort , 4s, 1963	5,130 95	
5,000	North American Co , Deb , 3½s, 1949	5,219 52	
5,000	Ohio Edison Co , 1st Mort , 4s, 1965	5,287 50	
4,000	Ohio Public Service, 1st Mort , 4s, 1962	4,240 75	
5,000	Pennsylvania RR, Gen , 4¼s, Series "E," 1984	5,013 10	
5,000	Philadelphia Company Collateral Trust S F , 4¼s, 1961	5,125 00	
2,000	U S Treasury, 4s, 1944/54	1,998 13	
50,000	U S Treasury Defense Bonds, Series "G," 2½s, 1953	50,000 00	
5,000	Virginia Public Service, 1st & Ref , 5½s, 1946	5,133 65	
<u>\$115,000</u>	TOTAL, Bonds	<u>\$105,449 20</u>	<u>\$10,875 00</u>

<i>Shares</i>	<i>Stocks</i>			
50	American Brake Shoe & Foundry Co , Conv , Pfd		6,163 60	
100	American Gas & Electric Co , 4½s, Cum Pfd		10,887 62	
50	Atchison, Topeka & Santa Fe, 5%, Pfd		4,970 75	
100	Chase National Bank of New York		4,550 00	
100	Curtiss-Wright Corp , Class A		2,652 80	
56	E I du Pont, \$4 50, Cum Pfd		6,868 34	
25	Eastman Kodak Co , Common		4,200 38	
75	General Motors Corporation, Common		3,594 53	
40	Great Atlantic & Pacific Tea Co , 7%, 1st, Cum Pfd		5,133 75	
50	Gulf States Utilities, \$6 00, Cum Pfd		5,625 50	
50	International Harvester, 7%, Cum Pfd	\$ 8,169 00		
100	International Nickel Co of Canada, Ltd		3,825 85	
10	Johns-Manville Corp , 7%, Cum Pfd	1,266 77		
50	Monsanto Chemical Co , \$4 50, Cum Pfd , A	5,878 60		
50	Montgomery Ward & Co , Inc		2,594 75	
150	Pacific Gas & Electric Co , 6%, Pfd		4,640 50	
50	J C Penney Co		4,084 90	
100	Phillips Petroleum Co , Common		3,978 80	
50	Timken Roller Bearing Co		3,407 25	
	TOTAL, Stocks	\$ 15,314 37	\$77,179 32	
	TOTAL, Investments	\$120,763 57	\$88,054 32	\$208,817 89

MINUTES OF THE BOARD OF REGENTS

ST PAUL, MINN

APRIL 24, 1942

The third meeting of the Board of Regents in conjunction with the Twenty-sixth Annual Session of the American College of Physicians convened in the Municipal Auditorium, St Paul, Minn, Friday, April 24, at 12 10 p m, with President James E Paullin presiding and Mr E R Loveland acting as Secretary, with the following members in attendance

James E Paullin	<i>President</i>
Charles H Cocke	<i>First Vice-President</i>
Henry R Carstens	<i>Second Vice-President</i>
William D Stroud	<i>Treasurer</i>
George Morris Piersol	<i>Secretary General</i>
Roger I Lee	
Charles T Stone	
J Morrison Hutcheson	
T Homer Coffen	
Ernest E Irons	
Hugh J Morgan	
James F Churchill	

President Paullin introduced Mr Russell Phillips, of the Philadelphia Chamber of Commerce, who, on behalf of Philadelphia, extended an invitation to the American College of Physicians to hold its meeting in that city in 1943 Mr Phillips presented not only a complete civic invitation, but one from the medical organizations, including the medical societies, medical schools and other agencies President Paullin thanked Mr Phillips and told him that the invitations would be duly considered later in the meeting, whereupon Mr Phillips retired

PRESIDENT PAULLIN We shall have a communication from Dr Hensel, Chairman of the local Committee on Publicity

DR CHARLES N HENSEL President Paullin, Regents and Officers, first of all I want to tell you what a delight it has been to meet you in this intimate way and to participate in your delightful and charming hospitality Secondly, I want to say to you that your Executive Secretary, Mr Loveland, and his cohorts have given us the most amazing and friendly cooperation Thirdly, I want to talk to you about the problems of the Chairman of the Committee on Publicity Since you have appointed a Chairman on Publicity I take it that you believe in regulating information for the press, and with that idea in mind I want to tell you some of the difficulties as a novice in this office that I have encountered

The first difficulty is the securing of current convention information to be given to the press The local Committee likes to feel that beginning three or four weeks before the convention an article shall appear each week in the press to inform the public of the coming convention, and that during the preceding week of the convention there should be three articles—one on Saturday, Sunday, and particularly on Monday morning This is where the difficulty arises It is extremely difficult to get that material We wrote to the men on the program asking for either the original paper or an abstract, and the response was practically nil Some of the articles furnished were not useful for publicity It occurred to us and I would like to make the suggestion that the Publicity Committee should have, before the convention started, abstracts of the papers to be presented on the program, these abstracts to be

released through the Executive Secretary's office, and transmitted to the local Chairman thirty days in advance of the meeting. These abstracts should be from three hundred to five hundred words, or two pages. This would enable the local Publicity Committee to release some material gradually to the press. This could be certified or supervised by the Program Committee so that you would know the kind of publicity that would be released. This is the thought that I would like to leave with you for your indulgence. (Applause)

PRESIDENT PAULLIN Thank you very much, Dr. Hensel.

The next item of business will be a review of the minutes of our preceding meeting held on Tuesday April 21.

Secretary Loveland read a review of the minutes of the meeting, which were approved as read.

PRESIDENT PAULLIN Dr. Cocke, since the recently-elected Chairman of the Board of Governors, Dr. Breed, is not present, will you kindly present a report?

DR CHARLES H COCKE Thank you, Mr. President. The Board had an interesting and active meeting. We had the good fortune to have Dr. Paullin with us and quite a lively discussion ensued, particularly relative to the matter of the present workings of the American Board of Internal Medicine.

It seems that there has been some criticism in various places, and as a result an animated motion was made by Dr. Walter B. Martin, Governor for Virginia, seconded by Dr. George Lathrop, Governor for New Jersey, that the Board of Governors request the Board of Regents to investigate the present workings of the examiners of the American Board of Internal Medicine to determine how they are operating and to recommend such improvements in their methods as they may think wise. The motion not only was carried, it was unanimously carried, and I submit it to you in Dr. Breed's absence, as my term of office as Chairman of the Board of Governors has expired. The election was held and Dr. William B. Breed was made Chairman.

PRESIDENT PAULLIN Would you mind stating, Dr. Cocke, some of the discussion that caused this resolution to be introduced? I think the Regents should know something of its background.

Dr. Cocke presented the details as taken from the minutes of the Board of Governors. Following its receipt there was general discussion and examples were presented by several, including Col. Hugh J. Morgan.

DR IRONS I think this a very good opportunity for the Board of Regents to be informed of some of the difficulties that the American Board of Internal Medicine has. I have no doubt that the Board of Internal Medicine has made mistakes, both of commission and omission.

When we began we had twenty-eight hundred applications for certification without examination. Four members of the American Board went over every one of these applications and all cases about which there was any question were submitted and voted upon by the full Board. It was a time-consuming procedure but we felt the

There is on every team of examination one member of the Board and a guest examiner who has nothing to do with the Board. It has been my observation that the guest examiner is inclined to be a little tougher on the candidate than the member of the Board. This oral examination does not represent the judgment of the Board alone, but also of the guest examiner. If there is any question or any doubt about the candidate's being passed he is given a blue card and is given another opportunity with a different examining team. Thus he has two chances. If the first team has been, perhaps, a little hard on the candidate, he has still another chance. Sometimes there is a difference of opinion between the first and second team, but most of the time the vote is unanimous. If there is any question concerning the man's record, what he has done, or concerning any of his qualifications, the whole Board reviews the case and leans backward to give him a square deal. I, too, have had experience with candidates whom I thought entirely capable and competent to pass the examinations, but who failed. They were so sure they were going to pass that they did not take their preparation seriously.

Now with respect to failures in Western New York. I do not know how many I may offend, if any, but there are a number of men who are educated in some of the schools in Western New York who have only a superficial knowledge of medicine. That, I think, explains the excess of failures from that particular district. We had a recent candidate up for examination who was both pompous and superficial. He had taken one of the previous examinations and failed. He came up this year a little subdued, and he produced better results. One of our guest examiners thought he again ought not to be passed because of his pomposity. We took the candidate to one side to talk to him, got him quieted down, and smoothed off some of his pomposity and finally passed him.

Another question has been raised in regard to the character of the questions. We are not going to fail a man because he does not know some of the very technical and unusual questions. However, we do not expect to ask a common garden variety of questions. We have plenty of practical questions and some a little abstruse. We use the latter because we want to know whether the man has a little of the background of medicine we should expect a future professor of medicine to have. This Board is not asking these men to join a social club. If they cannot meet the requirements they will have to come back later.

The Secretary of the Board is most efficient. His letters occasionally are technical, according to the By-Laws, arising from his absolute integrity.

PRESIDENT PAULLIN Does any member of the Board of Regents wish to speak?

DR ROGER I LEE Mr President, I think this is a very happy situation, and it indicates that men really want to join the College and to be certified. I have been hearing some criticisms of the Committee on Credentials and of the College which cheers me up a great deal because a man does not object unless he is rejected, and he does not kick unless he wants to get in. We shall have to take a certain amount of the bitter with the sweet, and I think that if physicians want to get in, and they are not all taken in as they might be in a social club, there is going to be a certain amount of complaint, which I think actually is a wholesome situation. The Board of Regents is the place to bring these matters up. I think there should be no action taken about these matters because this is a joint enterprise. We have the enterprise of our own Committee on Credentials. If we do not get some kicks we are not doing a good enough job, it seems to me.

DR IRONS Mr Chairman, I should like to add a word to Dr Lee's remarks. The American Board would feel if there were not some objections that there was something wrong with the Board.

PRESIDENT PAULLIN I feel that the American Board is doing a wonderful job.

The question is whether or not the Regents want to consider making a reply to the request of the Board of Governors. The request was that the Board of Regents investigate the present workings of the examinees of the American Board of Internal Medicine to determine how they operate and to recommend such improvements in their methods as may be thought wise. We cannot ignore that request of the Board of Governors. If you would like, we can designate some members of the Board of Regents to look into this and to report at the next meeting in December. What is your pleasure?

DR LEE. I would like to move that it be recorded in the minutes that the Board of Regents has discussed with great thoroughness this problem relating to the examinations of the Board of Internal Medicine and has voted to renew these discussions from time to time.

COL HUGH MORGAN. I second the motion.

There was no discussion, the question was called and the motion carried.

PRESIDENT PAULLIN. The next thing on the agenda is New Business.

DR PILRSOL. Mr. President, the Committee on Credentials recommends that from this date until further action by the Board of Regents, all Associates who are called to active duty with the armed forces of the United States shall have the time limit of five years for qualifying for Fellowship extended until they have been discharged from the armed forces. At that time they shall be allowed the same amount of time in which to qualify for Fellowship as remained to them when they entered the armed forces.

DR STONE. I second the motion.

The question was called and the motion carried.

PRESIDENT PAULLIN. Gentlemen, the next item of business is the election of the Secretary General. Do I hear any nominations?

DR COCKLE. I nominate Dr. Piersol.

DR COPIEN. I second the motion.

PRESIDENT PAULLIN. Are there any other nominations?

There were no other nominations, the question was called and the motion carried.

PRESIDENT PAULLIN. The Secretary will record the election of Dr. George Morris Piersol as Secretary General to succeed himself.

The next order is the election of a Treasurer.

DR HUTCHESON. I nominate Dr. William D. Stroud.

DR CHURCHILL. I second the motion.

PRESIDENT PAULLIN. Are there any other nominations?

COL MORGAN. I move that nominations be closed and Dr. Stroud be elected Treasurer.

DR COCKLE. I second the motion.

The President called the question and the motion was carried.

PRESIDENT PAULLIN. I declare Dr. Stroud elected Treasurer to succeed himself.

Next on the program is the appointment of 1942-43 committees. The Executive Committee consists of the elective officers and five Regents elected by the Board.

There was general discussion in which it was pointed out that the elective officers are automatically members of the Executive Committee. Nominations of the following were made, seconded and unanimously elected by resolution:

DR. STONE, C. D. D.

PRESIDENT PAULLIN The next committee is the Committee on Advertisements and Commercial Exhibits I re-appoint the Committee in its entirety

Dr George Morris Piersol, Chairman
Dr Sydney R Miller
Dr Charles C Wolferth

The next committee is the Committee on the ANNALS OF INTERNAL MEDICINE on which the term of Dr Reginald Fitz now expires I re-appoint him to membership on this Committee—the Committee consisting of the following

Dr Walter W Palmer, Chairman (1943)
Dr David P Barr (1944)
Dr Reginald Fitz (1945)

The next committee is the Committee on Constitution and By-Laws, a standing committee The President appoints one member each year

In view of the fact that Dr Ions' term expires this year and he is President-Elect, I will appoint Dr Charles H Cocke as Chairman of this Committee for the term 1945, and since Dr Samuel E Munson is retiring from the Board I will appoint Dr James D Bruce for his unexpired term The new committee is as follows

Dr Charles H Cocke, Chairman (1945)
Dr James D Bruce (1944)
Dr William J Kerr (1943)

The next committee is the Committee on Credentials Three of those members are appointed by the Board of Regents and three are appointed by the Board of Governors The Board of Governors has already appointed

Dr J Owsley Manier (1945)
Dr William B Breed (1943)
Dr Wallace M Yater (1944)

Dr Robert Cooke's term as an appointee by the Regents expires in 1942 and he has particularly requested that he be not re-appointed His is the only one whose term expires, and it has occurred to me that since Dr Charles H Cocke has been on this Committee from the Board of Governors for such a long period of time and is so familiar with the work that it might be well to keep him on this Committee as the delegate from the Board of Regents

COL MORGAN I so move

DR LEE I second the motion

PRESIDENT PAULLIN It has been moved and seconded that Dr Charles H Cocke be appointed for a term of three years (1945) on the Committee on Credentials

The question was called and the motion carried, thus constituting the Committee on Credentials as follows

Dr George Morris Piersol, Chairman (1943)
Dr Charles H Cocke (1945) Appointments by the Board of Regents
Dr Sydney R Miller (1944)

Dr J Owsley Manier (1945)
Dr William B Breed (1943) Appointments by the Board of Governors
Dr Wallace M Yater (1944)

PRESIDENT PAULLIN The next committee is the Committee on Educational Policy. This Committee is established by the Board of Regents. I re-appoint the members of the present Committee, but designate Dr. Irons as Chairman in the place of Col. Morgan, who is on active military service. The Committee, therefore, to be

Dr. Ernest E. Irons, Chairman
 Dr. Charles H. Cocke
 Dr. Hugh J. Morgan

There is the Advisory Committee on Postgraduate Courses, of which Dr. Edward L. Bortz has been re-appointed Chairman by the Board of Governors. The full personnel of this Committee as appointed by the Board of Governors is

Dr. Edward L. Bortz, Chairman
 Dr. C. Sidney Burwell
 Dr. Ernest H. Falconer
 Dr. Fred M. Smith
 Dr. James J. Waring

I also re-appoint the present College representatives on the Advisory Council on Medical Education, namely

Dr. Francis G. Blake
 Dr. Hugh J. Morgan

The Conference Committee on Graduate Training in Medicine has two delegates from the American College of Physicians, two from the American Board of Internal Medicine, and two from the Council on Medical Education and Hospitals of the American Medical Association. I re-appoint our two present representatives, namely

Dr. Hugh J. Morgan
 Dr. O. H. Perry Pepper

The next committee is the Committee on Fellowships and Awards. Dr. Irons has asked to be relieved from duties on this Committee, Dr. D. Slater Lewis is no longer a member of the Board of Regents, as is the case of Dr. Henry M. Thomas, Jr. I am re-appointing from the past Committee Drs. Blake and Fitz, and am appointing as new members Drs. Cotten, Carstens and Meakins, the full Committee to be:

Dr. Francis G. Blake, Chairman
 Dr. Henry R. Carstens
 Dr. I. Homer Cotten
 Dr. D. Slater Lewis
 Dr. Henry M. Thomas, Jr.
 Dr. O. H. Perry Pepper
 Dr. W. B. Fitz

The Committee on Nominations will be composed of

Dr William B Breed, Chairman
 Dr C W Dowden
 Dr James F Churchill
 Dr Hugh J Morgan
 Dr Fred M Smith

Drs Breed and Dowden are from the Board of Governors, Drs Churchill and Morgan are from the Board of Regents, and Dr Smith is a Fellow-at-large

Several years ago Dr Bruce appointed a Committee on Preparedness, which consisted of myself as Chairman and Drs Bortz, Irons and Lee. I think, perhaps, that Committee has fulfilled its usefulness to the College, and I see no use of continuing it. The Chair will entertain a motion that the Committee on Preparedness be discontinued.

DR STONE I so move

DR COCKE I second the motion

There was no discussion, the question was called, and the motion was carried.

PRESIDENT PAULLIN The Committee on Public Relations will consist of

Dr Roger I Lee, Chairman
 Dr David P Barr
 Dr A C Griffith
 Dr J Morrison Hutcheson
 Dr James E Paulin, ex officio

The Committee on Survey and Future Policy was abolished last year.

The Consulting Committee on Annual Sessions is an automatic committee and will consist of

Dr James E Paulin Chairman
 Dr George Morris Piersol
 Dr Roger I Lee
 Dr John A Lepak
 Dr James D Bruce
 Dr William B Breed

I re-appoint the members of the House Committee as follows

Dr William D Stroud, Chairman
 Dr T Grier Miller
 Dr Harry B Wilmer

At a previous meeting of this Board Dr David P Barr was re-appointed to the American Board of Internal Medicine for a three-year term expiring in 1945.

PRESIDENT PAULLIN We will now receive for the records a report from Dr Edward L Bortz, Chairman of the Advisory Committee on Postgraduate Courses for 1942.

Dr Bortz was unable to be present, but the following report was presented and made a part of the record.

"REPORT OF THE ADVISORY COMMITTEE ON POSTGRADUATE COURSES
 to the Board of Regents, American College of Physicians

"The following courses were conducted during the past year under the auspices of the American College of Physicians

	<i>Course</i>	<i>Fellows</i>	<i>Associates</i>	<i>Non-members</i>	<i>Number of Registrants</i>
No 1	ALLERGY Dr R A Cooke, Director	3	3	1	7
No 2	DIAGNOSIS AND TREATMENT OF HEART DISEASE Drs Paul White and Edward Bland, Directors	24	17	3	44
No 5	GASTRO-INTESTINAL DISEASES Dr Henry L Bockus, Director	15	13	7	35
No 7	ARTHRITIS AND RHEUMATIC DISEASES Dr Philip Hench, Director	22	13	8	43
No 8	PERIPHERAL VASCULAR DISEASES Dr E V Allen, Director	22	10	14	46
No 10	INTERNAL MEDICINE Dr Cecil Watson, Director	31	19	1	51
		117	75	34	226

"The following courses were cancelled, either by reason of lack of sufficient enrollment, or the removal, due to military service, of teachers from the staffs of institutions where courses had been arranged

	<i>Course</i>	<i>Fellows</i>	<i>Associates</i>	<i>Non-members</i>	<i>Number of Registrants</i>
No 3	GENERAL MEDICINE Drs William J Kerr, Stacy R Mettler, Arthur L Bloomfield and Dwight L Wilbur, Directors	1	0	1	2*
No 4	INTERNAL MEDICINE Drs Warfield T Longcope, George W Thorn, Maurice C Pincoffs and H Raymond Peters, Directors	13	3	4	20*
No 6	ALLERGY Dr Harry L Alexander, Director	1	0	1	2*
No 9	GASTRO-INTESTINAL DISEASES Dr Walter L Palmer, Director	2	5	6	13*
No 11	TUBERCULOSIS Dr James J Wiring Director	1	1	1	3*
		18	9	13	40

* These are registration figures at time courses were cancelled

"The Committee has had a meeting and discussed plans for courses to be offered during the 1943 winter and spring seasons. The Committee is of the opinion that the following courses should be offered

1 GENERAL MEDICINE, two weeks, Harvard Medical School

2 ALLERGY, one week New York, Dr Robert A Cooke

3 GENERAL MEDICINE one or two weeks, Philadelphia, Dr George Morris

Part of

PRESIDENT PAULLIN The next item on the agenda is a selection of the 1943 meeting place

DR COCKE Mr Chairman, I move we meet in Philadelphia

DR LEE I second the motion

PRESIDENT PAULLIN Are there any further nominations?

The Secretary, Mr Loveland, enumerated and presented a number of invitations. However, there were no further nominations, the question was called and the motion carried, selecting Philadelphia for the 1943 Session of the College

PRESIDENT PAULLIN The next general item of business is the appointment of a General Chairman by the Board of Regents

COLONEL MORGAN Mr Chairman, I would like to nominate an ideal General Chairman for our next Session in Philadelphia, in fact, I would like to qualify our going to Philadelphia by stating that we shall go if we can have this particular person as our Chairman. I refer to Dr George Morris Piersol. I feel keenly that his position there would insure a quality of meeting that would be the very best

DR BREED I second the motion

PRESIDENT PAULLIN Are there any other nominations?

DR BREED I move nominations be closed and that Dr Piersol be unanimously elected

The motion was seconded. President Paullin put the question and Dr Piersol was unanimously elected. (Applause)

DR PIERSOL I shall make every effort to insure that the meeting in Philadelphia, in spite of the difficulties with which we may have to contend, will be as good as the meetings we have held recently and in the past. Thank you very much

PRESIDENT PAULLIN Dr Piersol, the College is most fortunate in selecting you as its General Chairman

The next item of business is the selection of the date for the 1943 Session. It has been suggested by quite a few members that the meeting, if possible, should be held in the latter part of April, so that physicians could attend, during the same trip, the meeting of the American Congress of Physicians and Surgeons at Atlantic City the first week of May. It would save some members from the Far West a considerable amount of expenditure in time and money. Of course, it will have to be determined what dates are available in Philadelphia

SECRETARY LOVELAND It would be appropriate if this Board would give suggestions as to dates. We are not sure whether the Philadelphia Convention Hall is open the last week of April. We do know it is open the week of April 12. Perhaps this Board would like to authorize the General Chairman to set the week before the meeting of the Atlantic City Congress, if possible, or to adjust the date as near as possible to the wishes of the Board at some other time

There is much discussion among our members about the date of our meeting. Some still prefer a mid-winter meeting, as was customary several years ago. We changed from February because that appeared to be the most unsatisfactory month for our members in the South and Southwest. Some members object to an April or May meeting because there are so many other meetings at the same time. As a matter of fact during April, 1942, there were over thirty medical conventions scheduled in this country, and during May, over fifty

As soon as the date of our meeting is officially set it is my custom to notify the Secretaries of every national medical society and every state society of the dates, asking them, if possible, to avoid conflicts. Nevertheless, these announcements often are overlooked or disregarded, with consequent conflicts in meeting dates

DR LEE I move that the date of the 1943 Session in Philadelphia be left for selection to the President and the General Chairman

COLONEL MORGAN I second the motion

The question was called and the motion carried

DR PAULLIN The General Chairman and I would like to have some thoughts as to whether the Regents wish to change the date of the meeting, or if they still prefer the meeting in April

DR CHURCHILL Mr President, possibly I am more responsible for changing the date to April than any other man in the College It is a very serious matter for members in the Southwest to have the meeting as early as February Any time after the twentieth of March is satisfactory, but frankly, the men in the South and Southwest find it practically impossible to leave home in the middle of winter It is not fair or right to expect them to do so

PRESIDENT PAULLIN Is there any further discussion?

I feel, gentlemen, that the Board of Regents will take some official recognition to extend to the retiring President, Dr Lee, our vote of thanks for the untiring work he has done as the President of this College, for the tremendous amount of time he has given to the preparation of the current program, and for the success of this annual meeting I think we should extend to him our very sincere thanks and deep appreciation for what he has done, and also to the General Chairman, Dr Lepak, for the work he did in cooperation with Dr Lee This should be recorded in the proceedings of the Board of Regents and those of you who endorse these remarks will please stand

Everyone arose and the endorsement was unanimous

PRESIDENT PAULLIN Gentlemen, is there any further business to come before the Board? If not, I declare this meeting adjourned

The meeting was adjourned at 2 15 p m

Attest (Signed) E R LOVILAND,
Secretary

ANNALS OF INTERNAL MEDICINE

VOLUME 17

SEPTEMBER, 1942

NUMBER 3

PRIMARY COCCIDIOIDOMYCOSIS: A ROENTGENO- GRAPHIC STUDY OF 40 CASES *

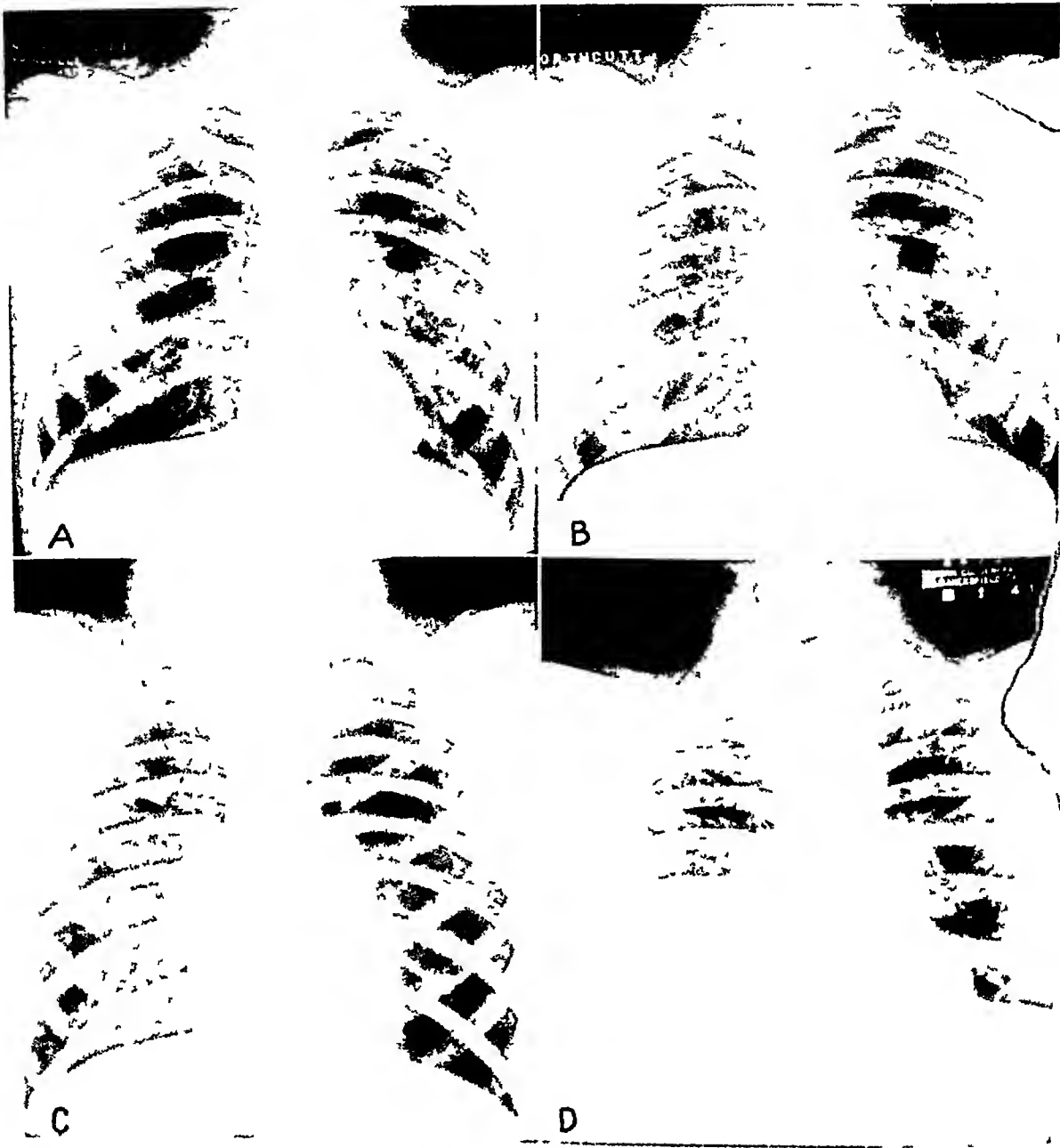
By WILLIAM A. WINN, M.D., and GILBERT H. JOHNSON, M.D.,
Springville, California

THE occurrence of coccidioidal infection within the human body was first described ¹ 50 years ago. For the next 45 years the disease was recognized in only its relatively fatal granulomatous form until Dickson in 1937 ² established the existence of a benign primary form of the infection. He also suggested the term, Coccidioidomycosis, which would apply to all types of infection produced by *Coccidioides immitis*. He further classified cases as due to primary coccidioidomycosis and to progressive (secondary) or granulomatous coccidioidomycosis. The basis for this distinction was the non-destructive type of reaction produced in the tissues by the first inhalation of the chlamydospores in contrast to the damaging granulomatous changes which develop during progressive secondary disease.

The mode of infection has been shown definitely to occur through the medium of dusty soil containing the chlamydospores of the fungus in its vegetative phase ³. General opinion in the literature has established that the chief portal of entry is the lungs as would be expected in an inhalation type of disease. Transmission from person to person or animal to animal is unknown.

The prevalence of coccidioidal infection in the vast inland San Joaquin valley of California, with its warm and dry climate, has been described by both Dickson ⁴ and C. E. Smith ⁵. The inhabitants of this area are considered to have become generally infected early in life or within the first year of their coming to the valley. Locally, the disease is recognized when associated with erythema nodosum as "Desert" or "Valley Fever". As the skin rash only occurs in 2 to 5 per cent of the cases of primary infection the majority of the residents are unaware of the actual time that they became infected. Farness ⁶ has recently pointed out the high incidence of coccidioidal infection in parts of Arizona and has justifiably ventured the opinion

* Read at the St. Paul meeting of the American College of Physicians April 24, 1942.



that the disease probably exists unrecognized in other areas where prevailing dryness of climate and soil conditions are favorable for the growth of the fungus. Shelton⁷ describes a new endemic area on the western slope of the Coast Range Mountains of California and the development of coccidioidal infection in 14 of a group of 736 soldiers within three months after their arrival at a military camp in this area. Davis et al.⁸ describe a small group epidemic in the Panoche Valley, immediately west of the San Joaquin Valley. They were able to isolate the fungus from the soil at the actual place where the infection occurred.

Persons of either sex at any age may contract the primary infection. The large number of migratory workers that entered the San Joaquin Valley from the middle west during the past six years have for the most part become infected by *Coccidioides immitis*. This, according to C. E. Smith,⁵ resulted in a proportionate increase of "Valley Fever" cases. A similar event is undoubtedly occurring among considerable numbers of military personnel transferred to this area for training. The opportunity for observing early manifestations of primary coccidioidomycosis will, therefore, be greater than usual during this particular period until all new residents of the valley have experienced their infections.

There are no pathognomonic symptoms of the initial coccidioidal infection.^{9,10} They closely simulate those of influenza or bronchopneumonia, or a severe "cold." General malaise with weakness, headache, muscle pains, pleurisy, cough, and gastrointestinal disturbances are common. There is accompanying moderate fever, and chills and night sweats may be present. Sputum accompanying the usual productive cough is small in amount, mucoid or mucopurulent, and frequently blood-streaked. Erythema nodosum or multiforme occurs in 2 to 5 per cent of the cases within eight to 14 days following the onset.

Complete histologic studies of the primary disease in human material are not available. Its exact nature has been suggested by the work of Cronkite and Lack,¹¹ who were able experimentally to infect 42 per cent of 72 guinea pigs by permitting them to inhale the chlamydospores. The resulting pulmonary infection, appearing eight to 21 days later, consisted of small grayish nodules, up to 5 mm in diameter, resembling the lesions of miliary tuberculosis. Histologically, they were fairly typical granulomata, involving interstitial spaces and showing little or no alveolar exudate. Mononuclear, epithelioid, and giant cells were present.

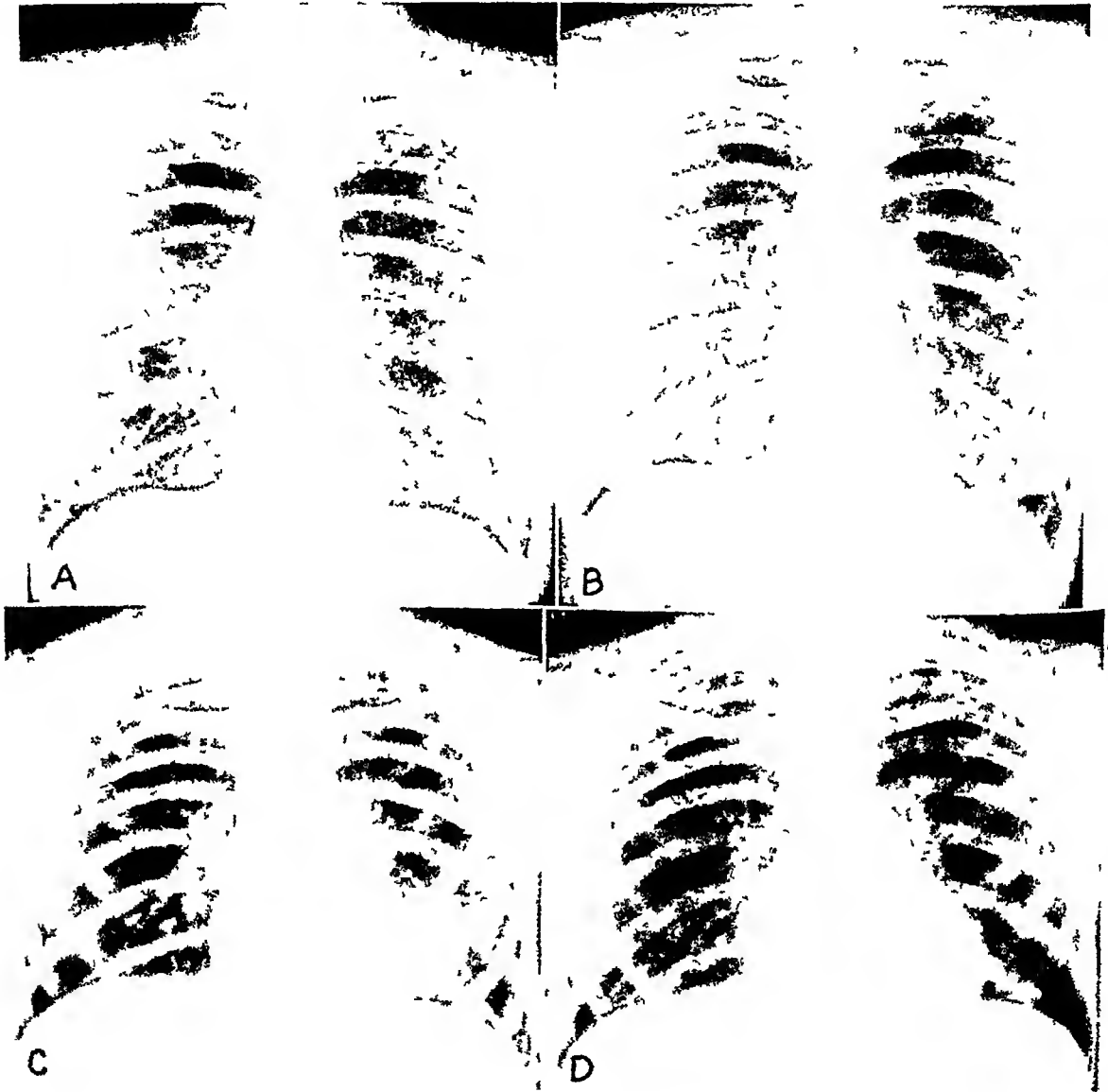
Roentgenographic observations of the manifestations of the primary stages of the pulmonary infection are not numerous. This is due, for the

This lesion had cleared completely three months later and patient made uneventful recovery.

D Patchy consolidation in lower half of right lung in a 35 year old American airplane mechanic. He came to the San Joaquin Valley one month previously from New York state. Sputum positive for *Coccidioides immitis*.

Lesion had completely cleared at the end of two months and patient made an uneventful recovery.

most part, to failure to suspect the existence of primary coccidioidal infection or to confusing it with "influenza," a "cold," or pneumonia. The patient may not even appear for medical care, unless he happens to develop erythema nodosum, which, as stated previously, is present in only one out of 20 cases.



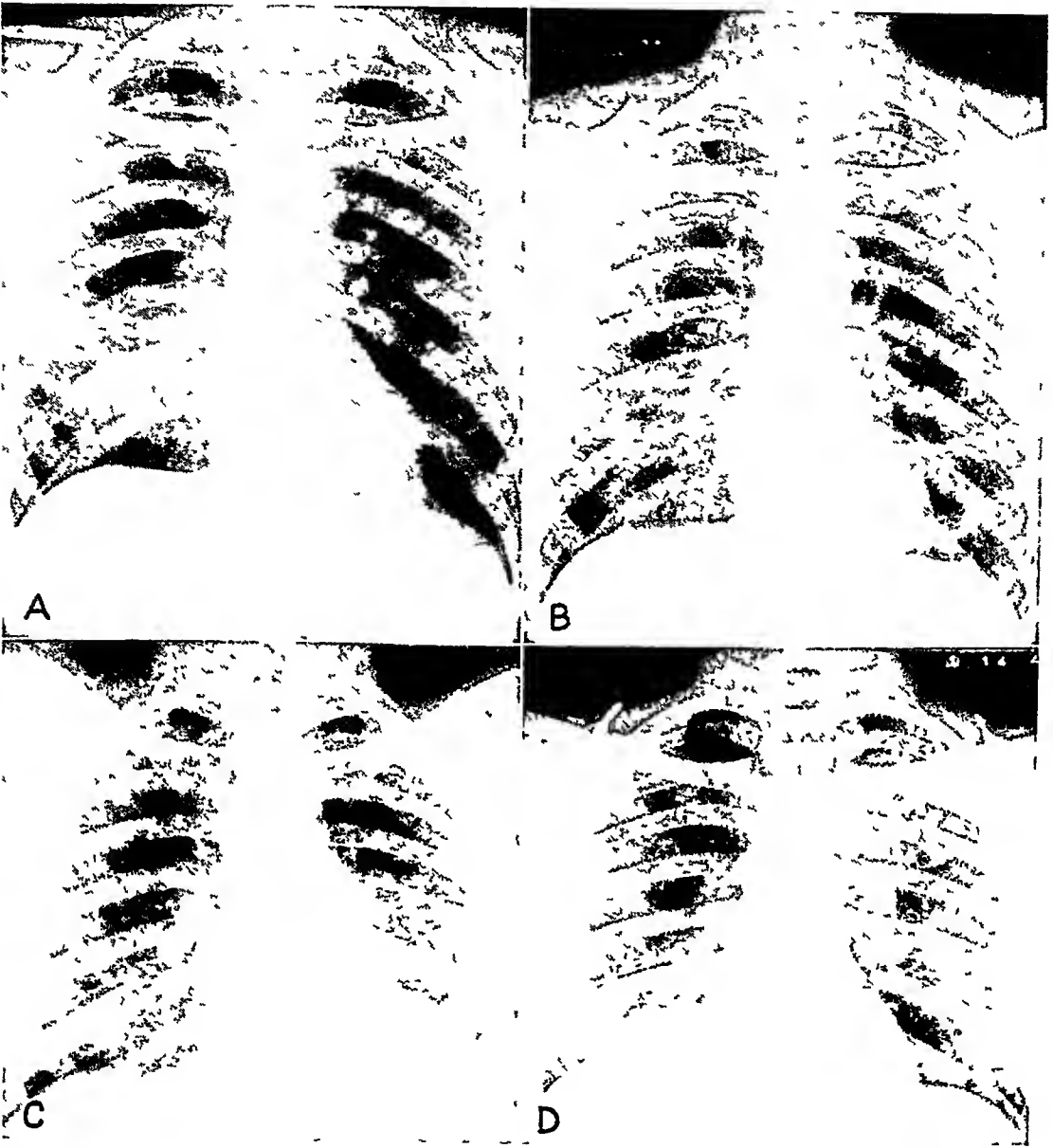


FIG 3 A Showing involvement of the lower half of the right lung in a 29 year old Negro

Sputum positive for *Coccidioides immitis*

Positive cutaneous reaction to 0.1 cc of 1:1000 coccidioidin

Resident of San Joaquin Valley for one year

B (Five years later) Showing small amount of residual fibrosis in right base Patient clinically well

C Illustrating exudative infiltration in base of the left lung with early enlargement of lymph nodes in upper left mediastinum appearing five weeks following the onset of an acute chest "cold" in a 27 year old American Negro

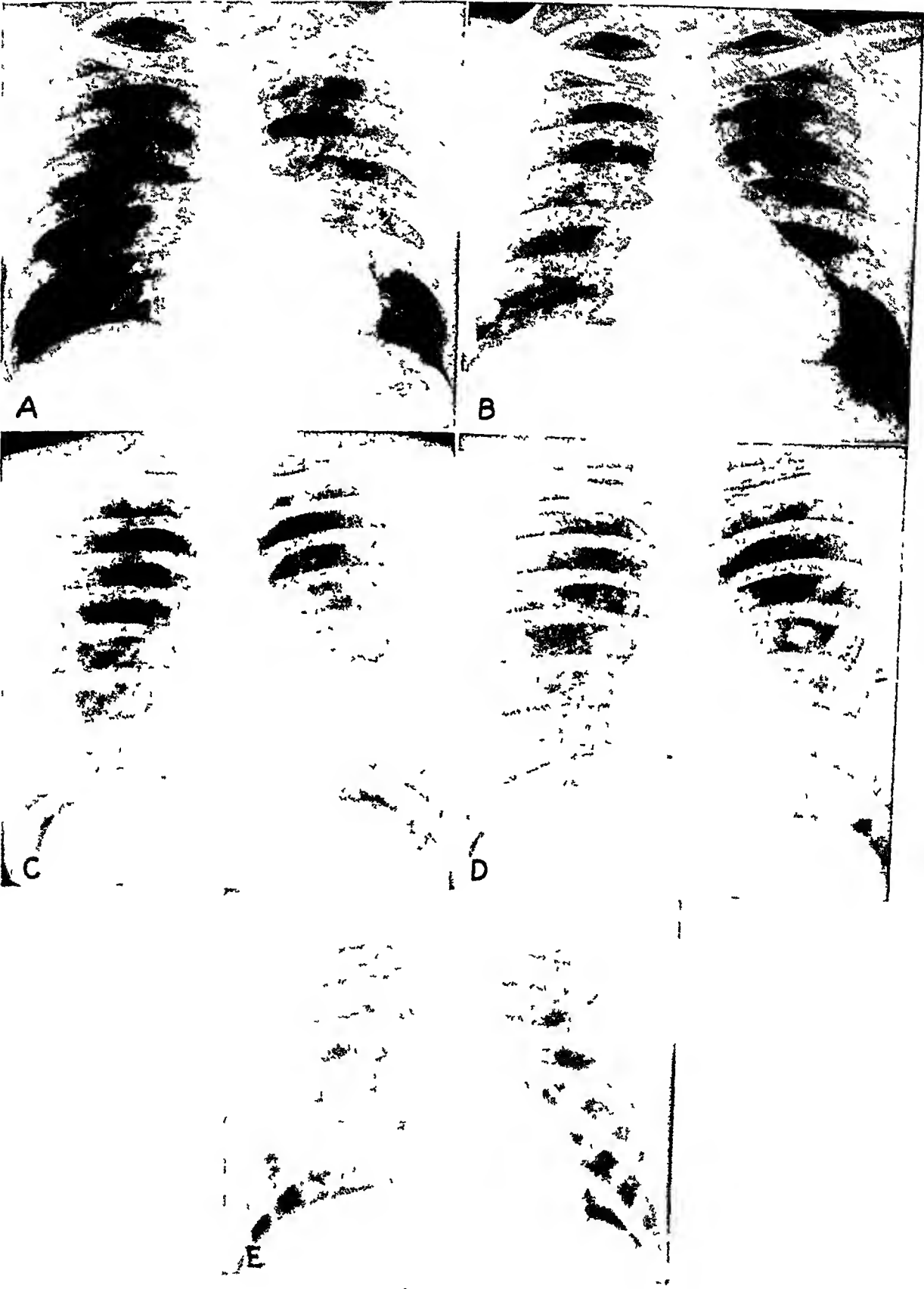
The patient died three months after the onset of present illness and autopsy revealed an abscess of the anterior end of the fourth rib on the left side with extensive pulmonary involvement and marked enlargement of hilus lymph nodes. Miliary abscesses also present in liver, spleen and kidneys. Pus from these loaded with *Coccidioides immitis*.

D Patchy exudative infiltration in the right base and above the left hilus in a 40 year old Negro who came to the San Joaquin Valley a few months prior to admission

Sputum positive for *Coccidioides immitis*

Strongly positive coccidioidin complement fixation and slightly positive precipitin

Death occurred from meningitis six months following admission



Unusual opportunities to observe the early roentgenographic development of the disease have occurred where infection occurred in the laboratory (Dickson⁹), and in an interesting group epidemic among seven college students recently reported by Powers and Starks¹². In the latter study it was concluded that the early lesions of primary pulmonary coccidioidal infection are usually solitary, though occasionally they may be multiple in number depending upon the degree of infection. The association of cavity formation was also described. Fairly persistent nodules were noted as a part of the pulmonary infiltrate, although the length of observation was not sufficient for possible calcification to occur within these. Each of the seven cases described made a complete clinical recovery. Faber, Smith, and Dickson,¹³ reporting on roentgenograms of the chest made in six children soon after the development of erythema nodosum, describe bronchopneumonic-like lesions, suggesting consolidation without lobar distribution. All lesions cleared in a few weeks' time, one forming small deposits of calcium two years later.

Carter¹⁴ has stated that "the detailed roentgen characterization of primary coccidioidomycosis must await repeated observation of many cases, over periods far past the time of clinical illness. This will come from the San Joaquin Valley."

We have observed 40 cases of primary coccidioidomycosis throughout the period of clinical illness and until the roentgenographic pulmonary features have either cleared, remained stable, or progressed. Admittedly, it will be necessary to repeat these observations over many more cases before we can

EXPLANATION OF FIGURE 4

FIG 4 A Illustrating scattered nodular productive lesions throughout the left lung field and outside the right hilus in a 29 year old Portuguese who had resided in the San Joaquin Valley for two years.

History of severe chest cold three months previously with persistent productive cough and night sweats.

Sputum positive for *Coccidioides immitis*.

Positive cutaneous reaction to 0.1 cc of 1:1000 coccidioidin.

Serological tests, positive complement fixation and precipitins.

B (Approximately one year later) Showing persistence of residual nodular foci in left lung field and outside of the right hilus. Almost complete clearing of left apex. Patient at work and clinically well.

C Calcifying fibrotic nodule lying outside and slightly below the left hilus in a 19 year old American girl who has resided in the San Joaquin Valley all her life. Picked up during roentgenogram survey of high school students. No history of acute illness other than "ordinary chest colds."

Positive cutaneous reaction to 0.1 cc of 1:1000 coccidioidin.

Negative cutaneous reaction to old tuberculin in 1:100 dilution.

D (Three and one half months later) Lesion becoming more discrete in appearance and of greater density.

E This single roentgenogram is representative of a large series showing a calcified parenchymal focus in a person who is clinically well and which probably represents a healed primary coccidioidal infection.

Note calcified lesion lying just above right costo-phrenic angle.

Patient 10 year old boy, born and raised in the San Joaquin Valley, who is in good health.

Positive cutaneous reaction to 0.1 cc of 1:1000 coccidioidin.

Negative cutaneous reaction to 0.1 cc of old tuberculin in 1:100 dilution (repeated) and to PPD second strength.

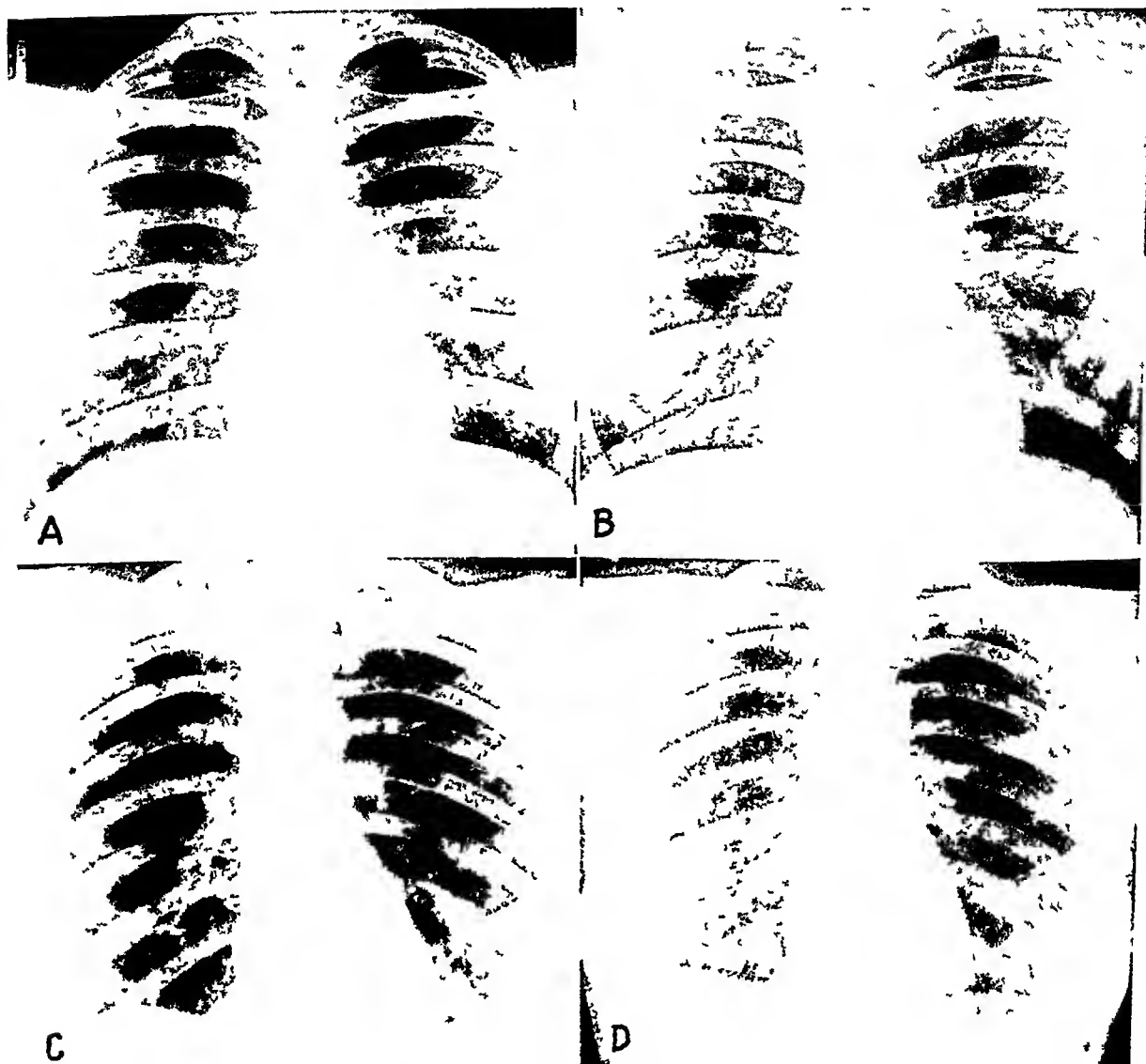


FIG. 5. A Infiltration beneath left hilus showing early development of small cavity in a 22 year old American tractor driver who has lived in the San Joaquin Valley all of his life. History of "flu" five weeks previously with pain in left side of chest, slight elevation of temperature and occasional productive cough. Sputum positive for *Coccidioides immitis*. Positive cutaneous reaction to 0.1 cc. of 1:1000 coccidioidin.

finally evolve a clear-cut understanding of the pathogenesis of the infection as revealed by serial roentgenographic observations. Recognizing the fact that the initial infection is for all practical purposes a pulmonary (Carter ¹⁴), only the primary manifestations as disclosed by roentgenography of the lungs will be considered.

From our series of cases we have selected certain ones as illustrating important roentgenographic aspects of the primary coccidioidal infection. It was possible in most instances to isolate *Coccidioides immitis* from sputum. Positive cutaneous reactions to coccidioidin were also present in each case. Serologic studies, in the majority of the patients, revealed the presence of circulating antibodies, and not only confirmed the diagnosis but were suggestive of the particular phase of the infection.*

Depending upon the amount of infection, acute primary coccidioidomycosis varies considerably in the degree of pulmonary involvement. A small nodular area of opacity may be all that is visible (figure 1 *a* and *b*); on the other hand there may be single (figure 1 *c*) or confluent (figure 1 *d*) areas of pneumonitis, more usual in the pulmonary bases. In many instances the lesions appear to be predominantly exudative in character and clear up rapidly (figure 2 *a, b, c, d*). Occasionally, they may leave a small amount of residual fibrosis (figure 3 *a* and *b*). In the Negro and Filipino, possibly owing to racial susceptibility, we have observed such primary exudative lesions to progress and result in early fatal dissemination of the disease (figure 3 *c* and *d*). There is a tendency for pulmonary foci of primary coccidioidal infection to assume the appearance of productive lesions, and to clear and decrease in size slowly and incompletely, leaving nodular densities that suggest caseation and that eventually may undergo calcification (figure 3 *a* and *b*). Solitary caseo-fibrotic foci undergoing calcification are illustrated in figure 4 *c* and *d*. Figure 4 *e* is illustrative of a large group of Hawaiian children with calcified pulmonary lesions, who have positive cutaneous reactions to coccidioidin (0.1 c.c. of 1:1000 dilution) and negative reactions to both old tuberculin (down to and including 0.1 c.c. of 1:100 dilution) and to purified protein derivative (second strength). Here, as in primary tuberculous infection, calcification represents a focus of previous coccidioidal infection.

Cavity formation accompanying the early acute phase has been described (Farness and Mills,¹⁵ Powers and Starks,¹² and Winn¹⁶). Such cavities are usually single, may close spontaneously (figure 5 *a* and *b*). There is, however, a marked tendency for them to persist, despite regression of the surrounding pulmonary lesions (figure 5 *c* and *d*). They then assume a characteristic thin-walled and cyst-like appearance with little or no surrounding collapse.

* For most of the bacteriologic confirmation and all of the serologic studies we are indebted to Dr. C. E. Smith and staff of the Department of Public Health, Stanford University School of Medicine. The results of his studies on the serology of coccidioidal infection will be reported in a forthcoming paper. They indicate that precipitins, often marked during the early initial infection, decrease with healing and that complement is fixed only in high dilutions. With dissemination of disease, however, complement fixation apparently rises.



reaction, and change little in size, shape, or appearance over a period of several years. Such cavitation may also be multiple (figure 6 *a* and *b*). Although these cavities serve as reservoirs for the existence and growth of *Coccidioides immitis*, manifested by the continued presence of endosporulating spherules in the sputum, they apparently cause no injury to the health of the person. They are frequently the source of small repeated hemoptyses which may be the only factor leading to their detection.

Localized bronchiectasis may also result from coccidioidal infection, and in one patient an indolent and benign bronchiectatic process was discovered in the right apex, which progressed very slowly over a period of 11 years. Associated clinical manifestations were slight, consisting only of rare blood-streaked and scanty sputum, and the patient remained in good health (figure 6 *c* and *d*).

Initial infection is sometimes manifested by a primary pleuritic effusion, no different from that seen in latent tuberculosis, with the exception that *Coccidioides immitis* may be recovered from the fluid (figure 7 *a* and *b*). As observed by us in one instance, complete absorption of the fluid occurred, with reexpansion of the underlying lung and no residual evidence of the infection other than slight pleural thickening.

Roentgenographic evidence of secondary mediastinal or hilar adenopathy in association with primary coccidioidal infection is infrequent, although it may occur. Such visible adenopathy has, in our experience, proved a sign of ill omen, preceding fatal dissemination of the disease.

It is unusual for primary coccidioidomycosis to become a progressive disease. When it does so it may assume either an acute or chronic course as it disseminates. Distribution suggests systemic seeding via the blood stream, with entry into the stream occurring from involved lymph nodes. Hence, the serious implication of advancing adenopathy following the initial infection.

Acute disseminating primary coccidioidomycosis is probably always fatal. In our experience the illness may run its course in from five weeks' to seven months' time. The most virulent infection of this type that we have seen occurred in a 36 year old Filipino, and was of miliary type and distribution, associated with multiple verrucous skin lesions over the face, upper trunk, and extremities (figure 7 *c* and *d*). Death occurred five weeks after the onset of the illness, and necropsy disclosed miliary nodules throughout the lungs, spleen, and liver.

C A 25-year-old American housewife who has complained for the past 11 years of a persistent and slightly productive cough with occasional blood-streaked sputum.

Since the first roentgenogram made 10 years ago there has been slowly progressive fibrosis and bronchiectatic-type change in the right apex, as disclosed by this film.

Sputum now positive for *Coccidioides immitis*.

Positive cutaneous reaction to 0.1 cc of 1:1000 coccidioidin.

Coccidioidin complement fixation markedly positive.

D Instillation of iodized poppy seed oil partly outlines sacculated bronchial defects in the right apex, verified by fluoroscopy.

Impression: Localized apical bronchiectasis of coccidioidal type.



A



B



C



D



D

Prominent mediastinal or hilus adenopathy followed by dissemination is illustrated in figures 8 and 9. Necropsy disclosed extensive disease, sometimes associated with meningitis.

Chronic disseminating coccidioidomycosis (coccidioidal granuloma) has a 50 to 60 per cent mortality. This form, characterized by the frequency of accompanying extrapulmonary lesions and the tendency toward abscess formation, was for 45 years the only recognized form of coccidioidal infection. Its pathology has been well described by Ophuls,¹⁷ and the roentgenographic appearance by Carter.^{14, 18, 19}

SUMMARY

The roentgenographic features of the pulmonary pathologic changes produced by primary coccidioidomycosis, both retrogressive and progressive, have been described. Our deductions are based upon the close observation of 40 cases of primary coccidioidal infection, in which the course of the infection has been outlined by serial roentgenographic and clinical follow-up studies.

The different types of exudative and productive pulmonary lesions have been described, as well as the tendency of the primary form of the disease to heal. Attention has also been called to certain pulmonary changes residual to primary coccidioidomycosis, including calcification and cyst-like cavities, the latter frequently associated with hemoptysis. Uncommonly, primary coccidioidal infection may become progressive, assuming either an acute or chronic (coccidioidal granuloma) form of dissemination, with an associated high mortality.

EXPLANATION OF FIGURE 7

FIG 7 A Hydropneumothorax and atelectatic lung in a 17 year old boy who had resided in the San Joaquin Valley for four years.

Culture of the slightly turbid fluid removed from the chest revealed an abundant growth of *Coccidioides immitis*, confirmed by animal inoculation.

Positive cutaneous reaction to 0.1 cc. of 1:1000 coccidioidin.

Negative cutaneous reaction to 0.1 cc. of 1:100 old tuberculin.

B (Fifteen months later) Lung expanded and no evidence of definite parenchymal lesion.

Serological tests markedly positive complement fixation at first, later becoming weaker with clinical improvement.

C Illustrating consolidated area in base of left lung and finely stippled infiltration throughout the remainder of both lung fields of miliary type. Note pleural calcification on right side. This occurred in a 36 year old Filipino vineyard worker, who had resided in the San Joaquin Valley for six years. There were extensive multiple verrucous skin lesions on the face, back and extremities.

Death occurred five weeks after onset of present illness. Autopsy disclosed disseminated disease of miliary type without gross lymphadenopathy.

Sputum and serum from skin lesions contained spherules of *Coccidioides immitis*.

Serological tests strongly positive complement fixation and precipitins indicating acutely disseminating primary infection.

Patient gave negative reactions to coccidioidin and old tuberculin down to 1:10 dilution, (anergic).

D Showing appearance and distribution of verrucous skin lesions.

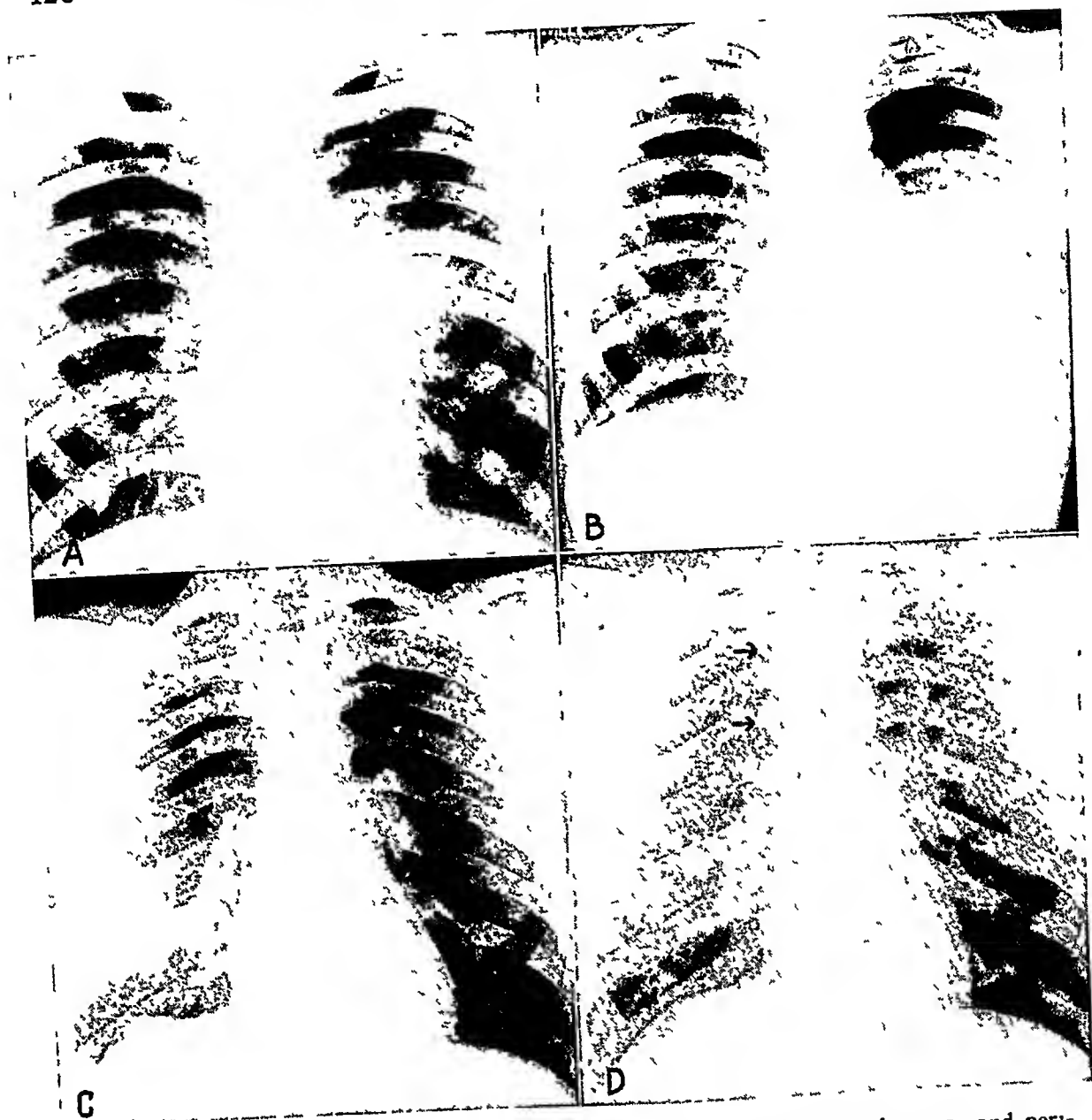


FIG 8 *A* Marked left hilus lymphadenopathy with some peri-hilar haziness and peri-bronchial infiltration in the left base in a 13 year old American school boy who had resided in the San Joaquin Valley for two years. There were associated erythema multiforme-like lesions of unusually chronic type.

Sputum positive for *Coccidioides immitis*.

B (One month later) Artificial pneumothorax on the left discloses the mediastinal and hilus lymphadenopathy. Small pleural effusion positive for *Coccidioides immitis*.

Death seven months from onset of present illness with extensive disseminated milary disease, and enlarged caseous mediastinal lymph nodes at autopsy.

C Showing a dense rounded area of consolidation in the base of the right lung with some peribronchial infiltration in a 26 year old American bus driver who had resided in the San Joaquin Valley for 1½ years.

Sputum positive for *Coccidioides immitis*.

D (Two months later) Marked clearing of the density in the right base, but the appearance of lymphadenopathy above the right hilus. This was followed by death in two months from disseminated disease, including meningitis.



FIG 9 A Illustrating left pleural effusion and mediastinal lymphadenopathy in a 41 year old Filipino farm laborer who had lived in the San Joaquin Valley five years. History of four months' chronic cough and weakness. Sputum positive for *Coccidioides immitis*. Chest fluid negative. Note greatly enlarged mediastinal lymph node projecting outward from right border of upper mediastinum.

B (Eleven days later) Showing bronchogenic spread on the right and consolidation of the left lung in the lower half. Death occurred in six weeks from disseminated disease. Impression: Acute disseminated primary coccidioidomycosis.

C Illustrating areas of consolidation in the right upper lobe and base of the right lung in a five months old Negro infant. Note widening of upper mediastinum indicating adenopathy. *Coccidioides immitis* present in gastric contents and in pus from bone lesions. Impression: Acute primary progressive coccidioidomycosis.

D (Illustrating bone lesion) Showing multiple destructive bone lesions in the tibia, femur, fibula, ulna, skull and left metacarpal. Death in four months, autopsy disclosed abscesses in liver and spleen, and marked caseous mediastinal lymphadenopathy.

Recognition of primary coccidioidomycosis depends upon keeping the possibility of the disease in mind, especially if the patient gives a history of residency within an endemic area. Cases of suspected pulmonary tuberculosis, with persistently negative sputum, represent possible coccidioidal infection.

The coming of large numbers of uninfected persons, especially military personnel, into the inland California valleys and certain parts of Arizona and Texas, will result in a proportionate increase of the incidence of coccidioidal infection.

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VITAMIN B THERAPY IN PARALYSIS AGITANS *

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THE numerous therapeutic approaches to the problem of paralysis agitans indicate clearly the inherent difficulties in this problem. It is, therefore, only natural that several investigators have recently turned to vitamin therapy in the hope of finding a more effective weapon for attacking this apparently incurable disease.

It is noteworthy that of the six cases reported by Parkinson in his original essay on the shaking palsy one patient attributed his symptoms to over-indulgence in alcohol and another to a long period of neglect in a Spanish prison¹. Furthermore, Kikuchi states that monkeys with experimental B-avitaminosis develop mask-like facies, propulsive movements with forward stooping, occasional tremors and increased lacrimation with salivation². Finally, it was noted that among 50 pellagrins attending the nutrition clinic at Birmingham, 10 had extrapyramidal signs and five of these showed "mild Parkinsonism" without any antecedent history of encephalitis³.

Jolliffe administered pyridoxine in doses of 50 to 100 mg intravenously, either daily or every other day, to 15 patients with paralysis agitans. Four showed subjective and definite objective improvement. Two additional patients were subjectively improved. Of the 11 patients who showed no objective improvement, 10 had suffered disability for more than three years, and five of these gave a history of encephalitis^{4,5}.

Spies soon confirmed this observation and reported "dramatic improvement," particularly of the tremor, in patients having postencephalitic Parkinson's disease. In the arteriosclerotic group their results were not nearly so good⁶.

Jolliffe subsequently reported a group of 32 ambulatory patients with Parkinson's disease. In this latter group he noted that improvement seemed best in the postencephalitic group. In that group six of the 10 patients showed subjective improvement, all of whom were continuing treatment. Of these, however, only four showed objective improvement, and two had returned to work. In the idiopathic group six of the 16 patients showed subjective improvement, but only two objective improvement. He conservatively concludes that the syndrome of paralysis agitans seems to include people who are helped by pyridoxine⁷.

In a personal communication, it was learned that five of the 25 patients in Spies' clinic were showing improvement on pyridoxine therapy, but Bean⁸

* Received for publication August 8, 1941.

From the Neuropsychiatric Service of the Third (New York University) Division of the Welfare Hospital, New York City, and the Department of Psychiatry, New York University College of Medicine.

notes that some of his co-workers were not obtaining favorable results with other non-clinic patients

It was decided, therefore, to observe the effects of vitamin B therapy on a group of patients with paralysis agitans

Method Twenty-two unselected patients were used as subjects Of these four were idiopathic, 14 were postencephalitic, three were arteriosclerotic, and one was post-traumatic Their ages ranged from 28 years to 72 years, the average being 49.2 years The duration of symptoms varied from three years to 33 years, the average being 14.4 years It should, therefore, be particularly noted that we were dealing almost entirely with *very chronic* cases

The patients were then divided into two groups, comparable in type, age, and duration of symptoms One group of 12 patients was on the neurological service They received daily intravenous doses of the vitamin preparation The other group, comprising 10 patients, was not on the neurological service, and prior to the onset of the present study was composed of more or less ignored custodial cases They received daily injections of 5 c c of normal saline *

The vitamin preparations will be referred to as A and B †

Preparation A	Contents	Preparation B
10 mg	Thiamin chloride	10 mg
10 mg	Nicotinic acid amide	10 mg
1 mg	Riboflavin	1 mg
10 mg	Pyridoxine hydrochloride	100 mg
5 c c	Buffered solvent q s ad	5 c c

All patients were continued on whatever other therapy they were receiving prior to the onset of the experiment, so that any effects noted could be related to the added therapy Each case was carefully reexamined at the start of the experiment, and then again at weekly intervals until the experiment was completed The following points were then recorded on a special chart: Facies, condition of skin and hair, body attitude, gait, rigidity, strength (hand dynamometer measurements), speech, handwriting (timed), sleep habits, emotional status, and patient's evaluation of treatment

Each group received six intravenous injections a week The vitamin treated group received preparation A for five and a half weeks and preparation B for five weeks The control group received daily injections of 5 c c of sterile saline for ten and a half weeks Overenthusiasm was avoided The patients were all told that they were receiving vitamin treatment, and that we hoped it would help them

* Prior to the onset of the present experiment, both groups had received the usual treatments for paralysis agitans These included drugs of the atropine series, fever therapy, quinine, benzedrine, intramuscular B complex, thiamin and nicotinic acid intramuscularly, Rabellon and bellabulgara None of these therapeutic procedures had altered the course of the disease, but in some cases troublesome symptoms had been partially relieved

† Kindly supplied in sterile, single-dose "poly-B" ampoules through the courtesy of Dr H E Dubin, Technical Director of the U S Vitamin Corporation, New York

RESULTS

1 In both normal and control groups, it was noted that the symptomatology varied considerably from examination to examination, frequently from day to day, or even during the course of the same day

2 No objective changes were noted in the vitamin treated group Two of these patients claimed subjective improvement, but showed no objective change One, chair-fast for the previous year, disliked her injections so much that she sought to avoid them by walking to the bathroom each morning Otherwise, she showed no objective change for the better None of the patients in this group was enthusiastic about the treatment One patient developed intestinal obstruction (volvulus) during the course of the treatment, necessitating operation He eventually died of postoperative pneumonia

3 Nine of the control group were very enthusiastic about the effects of the treatment for the first two weeks, but thereafter only three persisted in their subjective improvement One of these patients, who had been incontinent and bedfast, began to get up daily and walk to the bathroom, a distance of 75 yards He showed no other objective improvement Interestingly, he had performed similarly while receiving whole belladonna root therapy for the first time the preceding year

4 Three partially bald males receiving the vitamin preparations showed a regrowth of fine lanugo hair over the vertex One female, whose hair had been falling out, said that this ceased after two weeks of therapy Spies noted similar results with nicotinamide⁹

5 Beneficial results in insomnia have been noted with vitamin B₆⁹ This was not apparent in our cases, and insomnia continued to be a troublesome symptom to about two-thirds of our patients

DISCUSSION

In evaluating the results of vitamin therapy in a group of patients suffering from any chronic illness, the following factors must be kept in mind

A The Specific Vitamin Action of the Material Used There is no evidence indicating that paralysis agitans is causally related to any specific vitamin deficiency There is at the present time a particularly great need for more expert laboratory technics Of course, we do not suggest that clinical experimentation should stop until these aids are available, but we do believe that clinical experimentation in this field will be much better directed, and the therapeutic results much easier to evaluate when these methods become available

B The Non-Specific Actions of Vitamins Vitamins are not only accessory foodstuffs, but also drugs Thus, nicotinic acid is not only a vitamin, but also a vasodilator drug Its vitamin and enzyme effects need bear no relationship to its use as a vasodilator drug In addition, thiamin, nicotinic acid and pyridoxine are pyridine derivatives, and riboflavin is easily

convertible into a pyridine. As such, the action of these substances may be on a purely pharmacological basis and need bear no relationship to their vitamin and enzyme properties.

C Psychological Factors It must be remembered that individuals attempt to maintain the experience of health even when threatened by a serious illness. The metabolic approach to these "degenerative" diseases has filled both patient and physician with a much needed optimism. In our patients the psychological effects of treatment were clearly demonstrable in our control group. These custodial cases, hitherto almost ignored, in general showed a better response to therapy than did our vitamin treated cases.

D Stage at Which Treatment Is Instituted Vitamin therapy to be efficacious must be instituted early. This is clearly demonstrated by the difference in the results from those previously reported by Jolliffe and Spies, who were in general treating cases of much more recent origin. Pathological processes are affected by therapy only when treatment is instituted before irreversible structural changes have occurred. This fact is worth the utmost consideration in evaluating therapeutic results and undoubtedly accounts for many differences in reported observations.

CONCLUSIONS

1 Twelve cases of long-standing paralysis agitans were treated with large amounts of the "B" vitamins and two showed subjective improvement. In no instance was there any objective change for the better.

2 Ten cases of long-standing paralysis agitans were treated with saline. Nine showed initial subjective improvement, and this persisted throughout the treatment in three instances. One of these latter showed objective improvement.

3 In the vitamin treated cases, three partially bald males showed some regrowth of hair. One female stated that her hair had ceased falling out.

4 Some of the difficulties in evaluating vitamin therapy in these cases are discussed.

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THE URINARY TRACT IN DIABETIC WOMEN; ITS CONTRIBUTION TO THE INCIDENCE OF HYPERTENSION *

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It has appeared to us that infection of the urinary tract has been a relatively frequent finding in diabetic patients, especially in women. Perhaps it is because numerous observations such as are cited in the following statements have brought this forcibly to our attention. An obese woman, who from past experiences should require little or no insulin to control the diabetes, is found to tolerate large doses. A search for a cause for this insulin resistance has often revealed a hidden infection in the urinary tract, treatment of which permitted a reduction of the insulin dosage. Further, when a diabetic patient, particularly a woman, is admitted to the hospital with fever, if the cause is not readily determined, the study of the catheterized specimen of urine often reveals it.

In diabetic women three unavoidable difficulties interfere with the diagnosis of infection of the urinary tract by routine clinical procedures. First, it is often impossible to differentiate between symptoms, either past or present, referable to diabetes and those caused by a possible urinary tract infection, secondly, even more important is the repeated observation that severe infection may be present without symptoms, and thirdly, it is well known that the interpretation of pus and bacteria in voided urine from the human female is commonly impossible, so that one can easily and conscientiously ignore even a report of "numerous white blood cells," especially if no symptoms are present. We, as those in other clinics, have hesitated to employ routine catheterization of the bladder and consequently have done this only when there appeared to be adequate reasons.

The following experience supports the concept that diabetic women are particularly vulnerable to infections of the urinary tract. During the past 15 months four diabetic women, who previously had not been under our care, were admitted to the Buffalo General Hospital with a history of chills and fever of short duration, all of them were profoundly ill, mentally confused and stuporous. Acidosis was not present. The *Bacillus coli* was cultured from the blood stream of three of the patients, and the *Bacillus*

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aerogenes capsulatus from the fourth. All of the patients had an obvious infection of the urinary tract, and the identical organism was found in the catheterized urine as was cultured from the blood. (These patients are not included with those in this report but will be the basis of a subsequent publication.)

Probably more important is the consideration of the influence of chronic infection of the upper urinary tract (chronic pyelonephritis) on arterial hypertension, a finding which is so frequently encountered in older diabetic patients, especially women. This was, of course, suggested to us by the recent contributions on that subject which have appeared in the literature.

PLAN OF STUDY

The Patients Studied Only women were observed, all between the age 36 to 79 years, three being under 40. The majority of the patients had been under our observation in a diabetic clinic for a considerable period. They were admitted to the wards for study, several each week, as they visited the clinic. Also, patients who were in the hospital for other reasons were included in the study. The diabetes was controlled at the time of the examinations. The study was done without consideration of suspected involvement of the urinary tract. Patients whose state was such that it seemed imprudent to subject them to the examination were rejected as subjects.

The Urologic Examination Before the cystoscope was passed the patients were asked to empty their bladder as completely as possible while in the sitting position. Then the presence or absence of residual urine was determined. If a stricture of the urethra was found, dilatation was carried out before cystoscopy. Specimens of urine were obtained from the bladder and kidneys for immediate microscopic examination, then, if cultures could not be made at once, they were placed in the ice box in the bacteriological laboratory. Renal function was determined by the injection of 1 c c of a standard phenolsulphonphthalein solution intravenously, urine specimens were collected from the kidneys and bladder at the end of one-half hour. The percentage of the dye in the transvesical leakage, when this occurred was divided and added equally to the percentages of the dye coming from the kidneys. All patients but one had a retrograde pyelographic study. In this one case an intravenous pyelogram was obtained. The out-patients remained in the hospital for 24 to 48 hours unless a post-cystoscopic reaction occurred which it did in a few instances but was never severe or serious.

The data obtained in 84 cases studied in the above manner have been placed in six tables each representing a group of cases. The patients were grouped in accordance with the involvement of the upper or lower urinary tract and those who showed abnormalities of the upper urinary tract were again subdivided with respect to the renal function as determined by the 'phthalein test. These divisions are explained in the headings of the tables.

KEY TO TABLES I, II, III, IV, V, VI

Retinal Arteriosclerosis The grades were defined as follows Grade 1, slight pressure of the arteries on the veins, uneven calibre and an increase in the light reflex stripe, grade 2, an increase in these changes, grade 3, evidence of advanced arteriosclerosis together with hemorrhages or exudates or both

Stricture of Urethra Stricture was considered absent when a cystoscope, No 24 F, could be passed freely Grade 1 stricture was held to be present when this instrument was passed with difficulty, grade 2, when it was necessary to start dilatation by a bougie of moderate size, grade 3, when it was necessary to start dilatation with a small bougie

Cystocele Grades 1, 2 and 3 (no qualification necessary)

Bladder "In" (signifies intensity of inflammation of the bladder) Grade 1, a trigonitis—an accentuation of the normal vascular distribution, a fusion of the capillaries and a loss of their individual characteristics, grade 2, when the inflammatory process was extended to involve the base of the bladder, grade 3, involvement of the entire bladder with redness, a loss of normal vascular markings, often with bullous edema and trabeculation "P" (pus in the urine) Grade 1, scattered leukocytes, grade 2, a visible sediment of leukocytes in the centrifuge tube, grade 3, marked pyuria "B" (bacteria in the stained smear) Grades 1, 2 and 3 (no qualification necessary)

Ureters and Kidneys "St" (stone in ureter) "Na" (narrowing of ureter) Grade 1, slight, grade 2, moderate, grade 3, extreme "Bl" (blunting of calyces) Grade 1, slight, grade 2, moderate, grade 3, extreme "B" (bacteria in stained smear, as under "Bladder") "P" (pus in urine, as under "Bladder")

Table I *Patients with Bilateral Reduction of Kidney Function* (group I) There were six patients in this group, five of whom had well established hypertension Cases 1, 2 and 3 had evidence of pyelonephritis with active infection on one or both sides at the time of the examination Infection in the upper urinary tract was either absent or minimal in cases 4, 5, and 6, but since blunting of the calyces and hydronephrosis were present in some degree on one or both sides it is possible that they had had pyelonephritis which had subsided A grade 2 or 3 retinal arteriosclerosis was present in four of the patients, the remaining two had cataracts

Table II *Patients with Unilateral Reduction of Function with Bilateral Urologic Lesions* (group II) There were 16 patients in this group, 13 of whom had hypertension Twelve had bilateral infection and in addition one, case 10, had complete obstruction of one ureter and infection on the other side Also, case 11 had or had had an infection on the left side where the 'phthalein excretion in one-half hour was but 3 per cent Similarly, case 13 probably had bilateral infection although the urine from the left side was not cultured, but there was evidence of extreme damage to the kidney pelvis and ureter and no 'phthalein was excreted Only case 15 in this group was completely free of evidence of infection in the upper urinary tract A retinoscopic examination was not carried out on one of the 16 patients, of the remaining, five had grade 2 and one had grade 3 arteriosclerotic retinitis Three had cataracts and one had glaucoma Four had normal fundi

Table III *Patients with Bilateral Normal Kidney Function and Bilateral Urologic Lesions* (group III) Fifteen patients comprised this group Eight of these had hypertension, although none had an extreme grade Nine had active infection on one or both sides In the remaining six cases there were various grades and combinations of hydronephrosis, hydroureter, and blunting of the calyces bilaterally Evidence of arteriosclerosis of the retinal

TABLE I
Patients with Bilateral Reduction of Kidney Function

Lower Urinary Tract						Upper Urinary Tract										
Case No	Age	Preg-nancies	B P Average		Retinal Arterio-sclerosis (Grade)	Structure Urethra (Grade)	Cysto-cle (Grade)	Residual Urine (cc)	Blad-der	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Dias												
1	48	3	185	100	Cata-racts	0	0	0	In -1, B -1	<i>B coli</i>	Na -1, Hy -2, St -1, B -2, B -3	11	<i>B coli</i>	Hy -1, B -0	2	0
2	58	0	204	94	3	0	0	30	P -3, B -3, In -3	<i>B coli</i> <i>Staph aur</i>	P -1, B -3	6	<i>B coli</i>	P -3, B -3	6	<i>B coli</i>
3	62	0	210	130	2	0	0	0	P -1	Enterococcus, <i>B aerogenes cap</i>	Hy -3, Bl -1, Pto-sis P -1, B -2	6	Enterococcus, <i>B aerogenes cap</i>	0	76	Enterococcus, <i>B aerogenes cap</i>
4	46	8	186	130	3	0	3	210	In -1, P -1	0	Hy -1, Bl -1	14	0	Hy -1, Bl -1	17	Anerobic strept
5	56	2	190	95	2	3	1	120	In -1, P -1	<i>B coli</i> , anerobic gram negative bac	P -1, Bl -1, Pto-sis	15	0	0	11	Anerobic gram negative bac
6	53	1	130	90	Left cata-ract	0	0	240 (?)	In -1,	0	Bl -1	15	0	Hy -2, Bl -3	16	0

TABLE II
Patients with Unilateral Reduction of Kidney Function and Bilateral Urologic Lesions

					Lower Urinary Tract					Upper Urinary Tract						
Case No	Age	Preg nancies	B P Average		Retinal Arterio-sclerosis (Grade)	Structure Urethra (Grade)	Cystocele (Grade)	Residual Urine (c c)	Cystitis	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Dias												
1	72	3	240	100	Early cataracts 1	1	1	0	In-0, P-1, B-3	<i>B coli</i>	P-1, B-0	24	<i>B coli</i>	P-2, B-3	7	<i>B coli</i>
2	67	1	190	90		0	1	180	P-1, B-1	<i>B aerogenes cap</i>	Hy-3, P-1, B-1	35	<i>B aerogenes cap</i>	Hy-3, P-1, B-1	16	<i>B aerogenes cap</i>
3	43	2	198	100	Glaucoma	3	3	0	In-1, P-1, B-1	<i>B coli</i> , enterococcus	Hy-2, P-1, B-1	15	<i>B coli</i> , enterococcus	P-1, B-1	25	<i>B coli</i> , enterococcus
4	72	—	150	80	0	0	1	90	In-1, P-1, B-1	<i>B coli</i> , enterococcus	Hy-2, P-1, B-1	15	<i>B coli</i> , enterococcus	P-1, B-1	25	<i>B coli</i> , enterococcus
5	59	11	155	90	Early cataracts	0	2	0	In-3, P-1, B-2	<i>B coli</i>	Hy-3, Bl-2, P-1, B-1	22	<i>B coli</i>	Bl-1, Hy-2, P-1, B-1	15	<i>B coli</i>
6	57	8	180	100	1	0	0	0	P-1, B-1	<i>Pseudomonas aeruginosa</i>	P-1, B-1	24	<i>Pseudomonas aeruginosa</i>	P-1, B-1	7	<i>Pseudomonas aeruginosa</i>
7	57	0	160	90	Cataracts	0	1	60	In-1, P-1, B-1	<i>B coli</i>	P-1, B-1, Bl-1, Hy ureter	16	<i>B coli</i>	Bl-2, Hy ureter	33	<i>B coli</i>
8	52	5	160	90	0	0	0	180	In-3, P-1, B-3	<i>B coli</i>	P-1, Hy ureter	8	<i>B coli</i>	0	25	<i>B coli</i>

TABLE II—Continued

					Lower Urinary Tract					Upper Urinary Tract						
Case No	Age	Preg-nancies	B P Average		Retinal Arterio-sclerosis (Grade)	Structure Urethra (Grade)	Cystocele (Grade)	Residual Urine (cc)	Cystitis	Culture	Right Ureter and Kidney	P S P % min	Culture	Left Ureter Kidney	P S P % 30 min	Culture
			Sys	Dias												
9	52	2	165	90	0	0	1	180	In-1, P-1	<i>Staph aur hem B coli, enterococcus</i>	Hy-1, Hy ureter	29	<i>Staph aur hem</i>	Bl-1	18	<i>Staph aur hem B coli, enterococcus</i>
10	64	8	200	120	3		1	180	In-3, P-3, B-3		Ptois, complete obstruction	—	—	P-1, dilated ureter	25	
11	59	5	190	100	1		1	0	In-1, P-2, B-3	<i>B proteus</i>	Hy-2, P-1, B-2, Bl-3, Hy ureter	37	<i>B proteus</i>	P-1, B-1	3	—
12	65	8	200	104	0		1	0	In-3, B-3	<i>B coli, Strept hem</i>	P-1, B-1, Hy-2	21	<i>B coli</i>	St-1, B-1, Hy-2	3	<i>B coli</i>
13	64	8	150	100	0		3	0	In-1	<i>Strept hem</i>	Hy-1, Bl-3, Hy ureter	26	<i>Strept hem</i>	Hy-1, Bl-3, Hy ureter	0	—
14	36	1	160	100	2		1	0	In-1, P-3, B-3	<i>B coli</i>	P-3, Hy-2, B-3, Bl-2, Na-1	13	<i>B. coli</i>	P-3, B-3	50	<i>B coli</i>
15	51	3	208	102	1		0	0	In-1, P-1	0		10	0	0	26	0
16	60	6	132	84	1		1	75	In-3, P-3, B-1	Enterococcus	P-1, Hy-2, Ptois	23	Enterococcus	0	7	Enterococcus

TABLE III
Patients with Bilateral Normal Kidney Function and Bilateral Urologic Lesions

					Lower Urinary Tract					Upper Urinary Tract						
Case No	Age	Preg nancies	B P Average		Retinal Arterio sclerosis (Grade)	Structure Urethra (Grade)	Cysto cele (Grade)	Residual Urine (cc)	Blad- der	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Dias												
1	52	4	130	80	0	0	1	70	P-1, B-1	Anerobic strept	Hy ureter P-1	28	Anerobic strept	P-1	26	Anerobic strept
2	61	1	155 160	80 90	Hazi- ness of lenses 3	0	1	0	In-2, P-1	0	Hy-1	22	0	Hy-2	35	0
3	46	3	165	95		0	2	60	In-1, P-1, B-1	<i>B coli</i>	St, Hy-1, Bl-2	26	0	P-1	27	<i>B coli</i>
4	49	6	130	80	Cata- racts	3	1	60	In-1, P-1, B-1	Enterococcus, gram neg gas pro- ducing bac	Hy-2	29	Enterococcus, gram neg gas pro- ducing bac	P-1	20	Enterococcus, gram neg gas pro- ducing bac
5	62	0	105	80	0	2	1	0	0	Gram pos cocci	Bl-1	25	0	Bl-1	22	0
6	48	6	150	80	1	2	3	0	In-1, P-1	0	Hy-1, ptosis, Bl-1	19	0	Hy-1, Bl-1	27	Hem strept
7	69	0	134	78	0	1 (car- buncle)	0	120	In-3, P-2, B-3	<i>B alka-lescens</i> , entero- coccus	P-1, B-1, Hy-1, Bl-1, ptosis, hy ureter	20	<i>B alka-lescens</i>	P-1, B-1, Hy-1, Bl-1, ptosis, hy ureter	19	<i>B alka-lescens</i>

TABLE III—Continued

Lower Urinary Tract							Upper Urinary Tract									
Case No	Age	Preg-nancies	B P Average		Retinal Arterio-sclerosis (Grade)	Structure Urethra (Grade)	Cysto-cele (Grade)	Residual Urine (cc)	Blad-der	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Dias												
8	59	5	180	80	0	0	1	300	In -1, (atonic bladder)	0	Hy -1, Bl -1, Hy ureter	34	0	Hy -1, Bl -1, Hy ureter	29	0
9	53	4	170	90	0	0	1	0	In -3, P -3, B -1 (atonic bladder)	B coli	Bl -1	33	0	Hy -1, Bl -1, Hy ureter, B -1, P -1	28	B coli
10	66	7	190	90	1	0	2	150	In -1, P -1	B coli, entero-coccus	Hy -1, Bl -2	23	0	Hy -1, Bl -1	19	Anerobic strept
11	48	18	140	95	0	0	3	0	In -3, P -3, B -3	B coli	Bl -2, Hy ureter, B -1	19	B coli	Bl -2, Hy ureter, B -1	26	B coli
12	61	2	134	70	0	0	0	15	In -3, P -2, B -2	Entero-coccus, Staph aur hem	P -1	20	Entero-coccus	P -1	25	Entero-coccus
13	45	3	150	100	0	0	1	0	In -2, P -1, B -2	B coli, Staph aur hem	B -2	28	Staph aur hem	0	25	Staph aur hem
14	55	1	180	90	1	0	2	0	In -1, P -1	0	Hy -2, Bl -2	28	0	Hy -1	23	0
15	56	2	170	90	2	0	2	180	In -2, P -3, B -2	B coli, Proteus morganii	P -1, B -1, Hy -3, Hy ureter	31	B coli, Proteus morganii	P -1, Hy -1	31	Proteus morganii

TABLE IV
Patients with Bilateral Normal Kidney Function and Unilateral Urologic Lesions

					Lower Urinary Tract					Upper Urinary Tract						
Case No	Age	Preg-nancies	B P Average		Retinal Arterio-sclerosis (Grade)	Stricture Urethra (Grade)	Cysto-cle (Grade)	Residual Urine (cc)	Blad-der	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Diast												
1	46	4	130	85	1	0	1	30	0	0	Hy-1, Bl-1, P-1, Bl-1	20	0	0	23	0
2	61	4	185	90	Cata-racts	3	3	80	In-1, P-1, B-3, In-1	B colt	Bl-1	23	B colt	0	29	0
3	79	3	200	100	2	2	3	120	In-1	0	Bl-1, ptosis	30	Anerobic gram neg bac	0	28	0
4	58	3	160	90	1	0	0	0	In-1, P-1, In-1	Anerobic strept	Bl-2	26	0	0	28	0
5	74	7	160	80	1	0	3	0	In-1	Anerobic strept	—	32	0	Bl-1, P-1	27	Anerobic strept
6	66	11	160	85	Cata-racts	2	3	0	P-1, B-1	Staph aur hem	St, Hy-1	28	0	0	27	0
7	48	16	130	82	0	0	1	0	In-1, P-1, In-1	0	P-1, B-1, Hy-2	36	B colt	0	35	0
8	43	5	150	95	0	0	1	0	In-1, P-1	Anerobic strept	Hy-2	27	0	0	26	0

TABLE IV—Continued

Lower Urinary Tract						Upper Urinary Tract										
Cree No	Age	Preg-nancies	B P Average		Retinal Arterio-sclerosis (Grade)	Structure Urethra (Grade)	Cysto-cele (Grade)	Residual Urine (cc)	Blad-der	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			S ₃ s	Dias												
9	56	7	150	110	0	0	3	0	In -1, P -1	<i>Strept hem</i>	Bl -1	25	0	Bl -1	24	<i>Strept hem</i> 0
10	45	2	146	90	0	0	1	0	In -2, P -1, B -3	<i>B coli</i>	Hy -2, Bl -1, P -1, B -1	25	<i>B coli</i>	0	23	0
11	38	5	122	84	0	0	1	0	In -2,	<i>B proteus, enterococcus</i>	0	32	Enterococcus	Ptosis	29	0
12	57	4	138	78	0	2	3	180	P -1, In -1, B -1	<i>Strept hem, anaerobic strept</i>	Hy -1, Bl -1, P -1	42	<i>Strept hem, anaerobic strept</i> 0	0	22	0
13	51	3	170	100	1	0	3	0	In -1, P -1	0	Hy -1, Hy ureter	26	0	0	24	0
14	51	8	130	70	0	0	0	30	In -1	<i>B coli, enterococcus</i>	Hy -2, Bl -2	4	0	0	30	0

TABLE V
Patients with Abnormalities Confined to the Lower Urinary Tract

			Lower Urinary Tract						Upper Urinary Tract							
Case No	Age	Preg nancies	B P Average		Retinal Arterio sclerosis (Grade)	Structure Urethra (Grade)	Cystocele (Grade)	Residual Urine (cc)	Bladder	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Dias												
1	65	0	190	90	0	2	0	0	0	Anerobic gram neg bac	0	29	0	0	22	0
2	68	14	180	90	1	3	3	150	In-3, P-3, B-1	<i>Staph aur hem</i>	0	20	0	0	20	0
3	68	7	128	90	Cataracts	3	3	135	In-3, P-3, B-3	Gram pos rods	Ureters not catheterized					
4	46	0	120	80	0	2	0	0	In-1, P-1	<i>B coli</i>	0	28	0	0	27	0
5	49	2	210	134	Corneal scars	2	1	0	In-1, P-1	0	0	32	0	0	25	0
6	51	0	120	75	0	0	0	0	In-1, P-1	0	0	38	0	0	43	0
7	62	10	135	80	0	3	3	60	In-1, P-1, B-1	<i>Strept hem</i>	0	33	0	0	22	0
8	63	0	210	105	1	3	0	0	In-1, P-1	Anerobic strept	0	26	0	0	25	0
9	53	8	142	80	—	3	3	0	In-1, P-1	Anerobic strept	0	26	0	0	25	0
10	60	3	190	100	1	0	1	600?	In-3, P-3, B-3	<i>B coli</i>	0	24	0	0	28	0

TABLE V—Continued

Lower Urinary Tract					Upper Urinary Tract											
Case No	Age	Prg-nancies	B P Average		Retinal Arterio-sclerosis (Grade)	Stricture Urethra (Grade)	Cysto-cele (Grade)	Residual Urine (c c)	Blad-der	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Dias												
11	62	2	205	105	1	0	1	100	P-1	Enterococcus 0	0	22	0	0	24	0
12	45	4	190	90	0	1	1	0	In-1, P-1	0	0	32	0	0	29	0
13	55	10	160	90	0	0	2	0	In-1, P-1	0	0	23	0	0	25	0
14	37	7	150	90	0	3	3	0	In-1, P-1	Anerobic gram neg bac 0	0	37	0	0	35	0
15	62	7	158	90	Cata-racts 1	0	3	30	0	0	0	24	0	0	23	0
16	70	0	134	82	0	0	0	0	In-1	0	0	24	0	0	30	0
17	61	0	138	78	Cata-racts 0	3	0	90	0	0	0	17	0	0	20	0
18	52	2	140	90	0	3	3	0	0	0	0	42	0	0	38	0
19	51	7	136	90	0	0	1	0	In-1, P-1	Enterococcus 0	0	27	0	0	25	0
20	58	1	170	100	0	0	0	0	In-1, P-1	Strept hem 0	0	22	0	0	18	0
21	48	2	130	80	0	3	3	180	In-2	0	0	20	0	0	20	0
22	58	1	204	104	1	3	3	0	In-2	0	0	20	0	0	20	0
23	47	2	170	90	1	0	0	90	In-1, P-1	Enterococcus 0	0	34	0	0	33	0
24	55	4	160	100	1	3	0	0	In-1	Strept hem 0	0	31	0	0	31	0
25	43	7	120	80	0	0	3	0	In-1, P-1	0	0	30	0	0	32	0

TABLE VI
Patients with Normal Urinary Tracts

Case No	Age	Preg nancies	Lower Urinary Tract					Upper Urinary Tract								
			B P Average		Retinal Arterio sclerosis (Grade)	Stricture Urethra (Grade)	Cystocele (Grade)	Residual Urine (cc)	Bladder	Culture	Right Ureter and Kidney	P S P % 30 min	Culture	Left Ureter and Kidney	P S P % 30 min	Culture
			Sys	Dias												
1	44	1	138	80	0	0	0	0	0	0	0	23	0	0	28	0
2	48	4	170	80	1	0	0	0	0	0	0	20	0	0	20	0
3	46	4	120	85	0	0	0	0	0	0	0	41	0	0	33	0
4	46	4	119	80	0	0	0	0	0	0	0	27	0	0	8	0
5	70	8	130	70	0	0	0	0	0	0	0	26	0	0	20	0
6	47	1	130	88	0	0	0	0	0	0	0	31	0	0	31	0
7	53	4	150	80	1	0	0	0	0	0	0	28	0	0	28	0

arteries was found in five patients, in three of the patients its severity was grade 1, in one patient, grade 2, and in one patient, grade 3. Cataracts were present in two patients.

Table IV Patients with Bilateral Normal Kidney Function and Unilateral Urologic Lesions (group IV) Fourteen patients fell in this group. Eight of these were judged to have hypertension. In five the unilateral disturbance was an active infection whereas in the remaining cases the evidence pointed to a residuum of probable past involvement. One patient had a stone in the ureter. Four had retinal arteriosclerosis, grade 1, and one, grade 2, two had cataracts.

Table V Patients with Abnormalities Confined to the Lower Urinary Tract (group V) Thirteen of the 26 patients who had involvement of the lower urinary tract only had hypertension. None of these had advanced sclerosis of the retinal arteries. Nine were judged to have grade 1 sclerosis. Three had cataracts, one corneal scars, and the retina of one was not examined.

Table VI Patients with Normal Urinary Tracts (group VI) Only seven patients in this series of 84 diabetic women were completely free of pathologic changes in the urinary tract. Two of these were classified as hypertensives, but there was an increase in the systolic pressures only. Both of these had evidence of a slight sclerosis of the retinal arteries.

Stricture of the Urethra, Cystocele and Residual Urine It seemed reasonable to suppose that the presence of stricture of the urethra, cystocele

TABLE VII

Summary of the Incidence of Hypertension, Retinal Arteriosclerosis and Upper Urinary Tract Infection in the Various Groups

Groups	Average Age	Number of Patients	With Hypertension	Advanced Retinal Arteriosclerosis	Active Upper Tract Infection	Evidence Suggesting Past Infection
I Bilateral reduction of kidney function	54	6	5	4 (cat 2)	3	3
II Unilateral reduction of function with bilateral lesions	58	16	13	5 (cat 3, glau 1)	13	2
III Normal kidney function bilaterally with bilateral lesions	55	15	8	2 (cat 2)	9	6
IV Normal kidney function bilaterally with unilateral lesions	55	14	8	1 (cat 2)	5	3
V Involvement of lower urinary tract only	55	26	13	0 (cat 3)	—	—
VI Urinary tract entirely normal	51	7	2	0	—	—

and residual urine either alone or in combination might be conducive to bacterial growth, particularly when the urine contained sugar which might act as a favorable culture medium. Such factors might operate in much the same manner as prostatic obstruction in the male in the production of ascending infection. However, of the 51 patients who had various degrees of involvement of the upper urinary tract, caused chiefly by infection, only 17 had any degree of stricture of the urethra as compared with the presence of stricture in 16 of 26 patients who had only lower urinary tract lesions. It is to be added, however, that many of the patients in the lower urinary tract group were placed there solely because they had a urethral narrowing. Similar statements likewise apply to the occurrence of cystocele and residual urine. Many of the patients who were unable to empty their bladders completely had 'diabetic neuritis' so this failure might have had a neurogenic basis.

Pregnancies Since during pregnancy there is often sufficient pressure on the ureters to produce hydronephrosis and since 'pyelitis' of pregnancy is relatively frequent, data on the number of pregnancies were collected. Obviously it was impossible to get any accurate information on the incidence of toxemia of pregnancy. In looking over the tables it did not appear worthwhile to make any minute analysis of the influence of pregnancy on urinary infections. Only 10 of the women had not borne children. Of these 10 barren women five had definite infections of the upper urinary tract. It is possible that pregnancy was responsible for hydronephrosis or hydro-ureter in some of our patients. This seems unlikely, however, especially in those cases in which there was associated blunting of the calyces.

BACTERIOLOGY

Patients with Upper Urinary Tract Involvement (Groups I, II, III, IV) Fifty-one patients had abnormalities in the ureters or renal pelves or in kidney function as measured by the 'phthalein test, either on one or both sides. Of these, 34 had active infections in the bladder and in one or both renal pelves, which were quite regularly associated with hydronephrosis, hydroureter, narrowing of the ureter or stone. In some instances these occurred singly, but more frequently in combination. Of those which showed a growth of but a single organism these bacteria were found in the following instances: *Bacillus coli*, 14, *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*), 1, *Bacillus aerogenes capsulatus*, 1, *Staphylococcus aureus hemolyticus*, 1, *Bacillus proteus*, 1, *Streptococcus hemolyticus*, 2, *Enterococcus*, 3, anaerobic streptococcus, 2, *Bacillus alkalescens*, 1, and an anaerobic gram negative gas-producing bacillus, 1. When there was a double bacterial invasion the following combinations were found: *Bacillus coli* and *Enterococcus*, 3, *Enterococcus* and gram negative gas-producing bacillus, 1, *Bacillus coli* and *Proteus morgani*, 1, *Enterococcus* and *Bacillus aerogenes capsulatus*, 1, and *Streptococcus hemolyticus* and anaerobic streptococcus, 1.

Patients with Lower Urinary Tract Involvement Fourteen of the 26 patients in this group had pus in the bladder urine sediment and bacteria on culture. The following instances of infection were found: *Bacillus coli*, 2, *Enterococcus*, 3, anaerobic gram negative gas-producing bacillus, 2, *Streptococcus hemolyticus*, 3, *Staphylococcus aureus hemolyticus*, 1, gram positive rods, 1, and anaerobic streptococcus, 2. It appeared that when the *Bacillus coli* was the invading organism the upper urinary tract was more frequently involved.

Findings in the Pelves and Ureters of the Patients not Showing Active Infection There were 17 patients who were placed in the groups who showed some manifestation of an abnormality of the upper urinary tract but who did not have active infection. Only one of the patients was placed in those groups because she had a reduction of renal function alone. The remainder showed some degree of distortion of the calyces, hydronephrosis, hydroureter, narrowing of the ureter, stone or a reduction of function. These abnormalities were occasionally found only singly but frequently they were present in various combinations. The right side appeared to be involved in a greater number of instances and somewhat more extensively. We realize that these abnormalities might have been of little or no clinical significance and that probably they were evidences of a past infection or possibly of some mechanical interference, but since these abnormalities were so frequently found in the patients who had active infections they were regarded as definite disturbances.

Partial Control Series Since our diabetic patients showed infection and pathological changes of the urinary tract so commonly and since there was no report of a similar study of non-diabetic women with which we were acquainted, it seemed necessary that some sort of control be attempted. As we did not think it justifiable to subject normal women to complete urologic examinations the bladders of 24 women who were undergoing weight reduction in the obesity clinic were catheterized in the urologic department. The urine was examined for pus and bacteria immediately and then cultured. Twelve of them had a few leukocytes in the sediment, none had marked pyuria. Nine had a few bacteria in the smear and one was classified as having 'many'. Only six had a completely sterile urine, the bacterial flora was much the same as in the diabetic women who had involvement of the lower urinary tract. Three of the control women harbored *Bacillus coli* in the bladder urine.

DISCUSSION

The assembled material may be discussed under two distinct headings: first, the incidence of infection of the urinary tract in diabetic women and secondly, the rôle of infection of the upper urinary tract in these cases in the production of arterial hypertension.

There is little available literature on infection of the urinary tract of normal healthy women. Leishman¹ found seven of 100 people (50 men

and 50 women) to have *Bacillus coli* in the urine. We studied the catheterized specimens of urine from 24 unselected, obese, non-diabetic women, none of them was found to have marked pyuria and only one had numerous bacteria in the smear. Our findings, therefore, make it appear probable that diabetic women do have a higher incidence of infection of the urinary tract than would be expected in normal women. Further it is questionable whether a few leukocytes and bacteria constitute a clinical infection, as it is well known that both the male and female urethras normally harbor bacteria, but the presence of bacteria and leukocytes in the upper urinary tract must be regarded as evidence of infection. Sharkey and Root² found 35 cases, 20 women and 15 men, in 196 consecutive necropsies with purulent infection of the urinary tract. They believed, however, that 74 per cent of these were of hematogenous origin caused by infection elsewhere in the body, and therefore their study is not comparable to ours. They commented on the susceptibility of diabetic patients to urinary infection, the chronicity of such infections, and the paucity of clinical symptoms which accompany this involvement. A recent unpublished study from the same clinic, by Baldwin and Root,³ which we have been given the privilege of examining and quoting, contains data from 143 additional necropsies on diabetic patients. In this group 21 per cent had infections (all types) of the upper urinary tract. The authors compare this incidence with large, general necropsy statistics, which probably included a small percentage of diabetics, in which the incidence of infection of the upper urinary tract was but 4 per cent.

From the standpoint of hypertension we believe that our group of patients are representative of any group of diabetic women who would be attending an out-patient clinic. Many of them were obese. They had been under our observation for varying periods, some of them for as long as 20 years. Their ages varied from 36 to 79 years. Under such circumstances a high incidence of hypertension would be expected. Beck and his co-workers⁴ made a survey in our clinic on hypertension in non-diabetic, obese subjects and in early diabetic patients, most of whom were women. Hypertension was found in 50 per cent of the diabetic patients and in 31 per cent of the obese patients. The average age of the diabetic patients, however, was 11 years greater. The incidence of well-established hypertension was about the same in the two groups and occurred at about the same age.

In the present series, of 33 patients—those belonging to the normal group and those who had involvement of the lower urinary tract only (Groups V and VI)—slightly less than 50 per cent had hypertension. The degree of retinal arteriosclerosis did not exceed grade 1 in any patient. Such a grade was present in 11 instances. In Groups III and IV, of the 29 patients who had unilateral or bilateral lesions but with normal function bilaterally, slightly more than 50 per cent had hypertension. Seven of the patients in these groups had retinal arteriosclerosis, grade 1, two had grade

2 and one grade 3 In Groups I and II, of the 22 patients who had reduced renal function on one or both sides, 18, or 82 per cent, had hypertension An ophthalmologic examination was made of 21 of these patients Five of them had cataracts and one had glaucoma so that the retina could not be seen Of the remaining 15, three had grade 3 retinal arteriosclerosis, three grade 2, and five grade 1

Pus cells and bacteria were found in 34 of the 51 patients who had involvement of the upper urinary tract either on one or both sides This finding was associated in the majority of cases with distortion of the calyces, as determined by retrograde pyelograms, hydronephrosis, hydroureter, narrowing of the ureter and a reduction of function either unilaterally or bilaterally These changes, of course, were found in various combinations Some of the patients who did not show infection at the time of the examination showed similar changes which might be interpreted as residua of healed lesions

The observations of a number of investigators make it appear that chronic pyelonephritis may be responsible for sclerosis of the vessels of the kidney, reduction of kidney function, and changes in the entire vascular system with hypertension Longcope and Winkenwerder⁵ and Longcope⁶ observed a group of 22 patients with chronic bilateral pyelonephritis over a period of several years and noted the development of arterial hypertension and retinal arteriosclerosis in 12 This occurred chiefly in women between the ages of 15 and 30 They believed that pyelonephritis often had its inception in acute pyelitis or more rarely an acute pyonephritis during childhood They commented that their patients did not commonly seek medical attention until symptoms of renal failure appeared In a recent monograph on pyelonephritis and its relationship to vascular lesions and arterial hypertension Weiss and Parker⁷ presented data on 100 patients with pyelonephritis The tables in their article contained clinical and pathologic information on 72 cases Of the 52 who had bilateral pyelonephritis 39 had hypertension and 30 died of uremia Twenty had unilateral chronic pyelonephritis, twelve of whom had hypertension and four of whom died of uremia (they died during an attack of bilateral acute pyelonephritis) Forty-nine of the 72 patients were women These patients represented a wide age variation The renal arterioles of the patients who had hypertension showed a high grade of productive endarteritis and hyperplastic arteriosclerosis and a few showed necrotizing arteriolitis Of the patients who had normal blood pressures the renal arterioles were involved, but to a lesser extent, and none of them had necrotizing arteriolitis They believe that pyelitis practically never occurs unaccompanied by pyelonephritis A complete bibliography accompanies their monograph

It therefore appears that pyelonephritis commonly progresses to the point where there is sufficient encroachment upon the kidney parenchyma to produce renal failure If this be the case, then we ask why diabetic pa-

tients, if they frequently have infection of the upper urinary tract, do not develop uremia more commonly. Renal failure, in our experience, is relatively unusual as a cause of death in diabetics. We have, however, observed a few instances in which diabetic women have died of uremia and hypertension which were clearly associated with pyelonephritis. Warren⁸ reports that in Joslin's Clinic from August 1922 to 1930, only 4.4 per cent of 1,294 deaths of patients who were diabetic were caused by nephritis. In the present group only three patients (the first three in Group I) were found to have any considerable degree of disturbance of kidney function as measured by the 'phthalein test. It is conceivable, however, that there may be infection of the upper urinary tract (chronic pyelonephritis) which progresses very slowly. Such an infection might cause sclerosis of the small vessels of the kidney and reproduce the Goldblatt⁹ experiment by causing a gradual throttling down of the renal circulation and subsequent ischemia, without serious damage to the kidney parenchyma within the lifetime of the patient.

SUMMARY AND CONCLUSIONS

Complete urologic examinations have been carried out on 84 unselected diabetic women between the ages of 36 and 79 without regard for complaints that would suggest trouble in the urinary tract. Some degree of involvement of the upper urinary tract was found in 51, abnormal findings in the lower urinary tract were found in 26, only seven had what was regarded as a completely normal urinary tract. The patients were grouped in accordance with the involvement of the lower or upper urinary tracts and those who had a disturbance of the upper urinary tract were subgrouped with respect to the renal function as determined by the 'phthalein test. A comparative study of the incidence of hypertension and of retinal arteriosclerosis was made in the various groups.

Leukocytes and bacteria were found in the renal pelves of 34 of the patients either on one or both sides. This finding was usually associated with other abnormalities of the urinary tract such as distortion of the calyces, hydronephrosis and narrowing of the ureter.

A variety of pathogenic bacteria was found, but the *Bacillus coli* predominated in those whose upper urinary tract showed infection. In the patients who had bacteria only in the bladder the *Bacillus coli* was less frequently found, otherwise, the bacterial flora was about the same as was found in the upper urinary tract group.

The patients who were found to have infections in the urinary tract frequently had no symptoms or at least none that would be differentiated from diabetic symptoms either past or present. It is believed that infections of the urinary tract in diabetic women often go undiagnosed because of the difficulty in the interpretation of the examination of urine from the human female. Catheterization under strict aseptic precautions is often justified.

Of 22 patients who had bilateral lesions or a reduction of function as measured by the 'phthalein test either on one or both sides 18 (82 per cent) had hypertension. Of 29 patients who had normal kidney function bilaterally but who had unilateral or bilateral lesions in the calyces, pelves or ureters, slightly more than 50 per cent had hypertension. Of thirty-three patients who had only abnormalities of the lower urinary tract or who had normal urinary tracts slightly less than 50 per cent had hypertension. Retinal arteriosclerosis was more frequent and was of a higher grade in those patients who had a reduction of kidney function either on one or both sides.

An extreme reduction of kidney function was found bilaterally in only three patients. The low incidence of renal failure as a cause of death in diabetic patients is commented upon.

It is suggested that in diabetic women there is frequently a slowly progressive pyelonephritis which may or may not produce a reduction of kidney function either bilaterally or unilaterally. This infection may in some cases be responsible for or contribute to the hypertension which is so common in older diabetic women.

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THE HYPERTENSINASE CONTENT OF PLASMA OF NORMAL, HYPERTENSIVE AND NEPHRECTOMIZED DOGS *

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THE pressor substance, hypertensin, was demonstrated by Braun-Menendez, Fasciolo, Leloir, and Muñoz ^{1, 2, 3, 4} of this Institute in the renal venous blood of ischemic kidneys and was shown to be identical with the pressor substance produced by the in vitro incubation of renin with blood globulins (hypertensin precursor) and unlike other known pressor substances. They concluded, therefore, that hypertensin is the pressor substance responsible for hypertension due to renal ischemia. Braun-Menendez and his collaborators ^{2, 3, 4, 5} likewise described a substance, hypertensinase, which destroys or inactivates hypertensin. Its distribution in the body, a method of its extraction from tissues, and a biological method for its assay have been described. The present report describes in detail certain modifications of the method of Fasciolo et al ⁵ to make it more applicable for the quantitative determination of hypertensinase in plasma and reports on the concentration of hypertensinase in plasma of normal, hypertensive, and nephrectomized dogs.

METHODS

Arterial blood was withdrawn from dogs using the usual precautions to avoid hemolysis, 0.1 volume of a 3.8 per cent solution of sodium citrate was used to prevent coagulation and the amount of dilution due to the citrate was taken into account in the calculation of the volume of plasma used for the determination of hypertensinase. After centrifugation, the amount of hemolysis in the plasma was determined roughly by means of the benzidine test. The color developing was compared with that produced by dilutions of packed red blood cells varying between 1:2500 and 1:40,000. Plasmas containing more hemolysis than one part in 5000 were discarded. Since Fasciolo et al ⁵ found 80 to 120 units of hypertensinase in 1 c.c. of washed red blood cells, the amount present in a 1:5000 dilution would be only approximately 0.02 unit which lies well outside the limit of error of the method.

All tubing, pipettes, etc., used in the preparation of solutions, were autoclaved or boiled. A testing solution was made up fresh as follows: standard hypertensin, 1 unit, M/2 NaH₂PO₄ (pH 7.4), 0.5 c.c., merthiolate (Lilly), 0.2 c.c., distilled water ad 8.0 c.c. To 8 c.c. of the testing solution in seven

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test tubes were added exactly 1.5, 1.0, and 0.5 cc of undiluted plasma, and 1.5, 1.0, and 0.5 cc of plasma diluted 1 to 4 with distilled water. The seventh tube was used as a control. The volume of each tube was made up to 10 cc with distilled water. At first, a second control tube consisted of 8 cc of the testing solution and 2 cc of plasma the hypertensinase content of which had been destroyed by changing the pH to 3.9 for 20 minutes at 37° C and then neutralizing. This was later omitted, however, because the same value was always obtained as in the control tube using water instead of plasma.

DETERMINATION OF HYPERTENSINASE. 4 HOUR INCUBATION

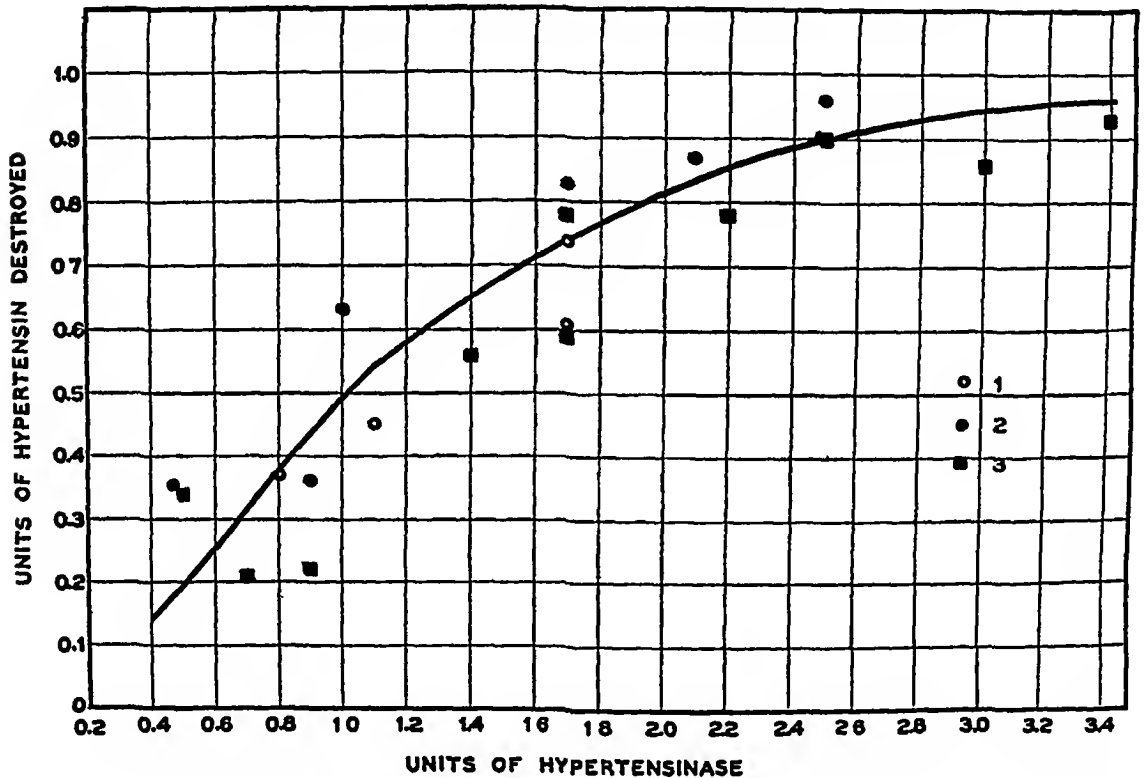


FIG 1 The destruction of hypertensin by hypertensinase during four hours of incubation at 37° C. Dots, circles, and squares represent experiments on different days.

The tubes were incubated in a water bath for two hours at 37° C and then placed in boiling water for 10 minutes to destroy the hypertensinase present. The solutions were injected intravenously into dogs of about 10 kilos anesthetized with chloralose or nembutal. The amount of hypertensin present in each tube was determined according to the method of Braun-Menendez, Fasciolo, Leloir, and Muñoz⁶. The amount of hypertensin destroyed by the hypertensinase was calculated by subtracting the amount found from 1.0 unit which was the amount of hypertensin originally present in each tube. From the amount of hypertensin destroyed, the amount of hypertensinase present was calculated from the curve of figure 2.

RESULTS

Two and Four Hour Incubation Curves Fasciolo et al⁶ defined the unit of hypertensinase as the amount which in a volume of 10 c c destroys 0.5 unit of hypertensin in four hours at a temperature of 37° C. A solution of hypertensinase was prepared from liver as described by Fasciolo et al, and the amount present was determined by the method described on three occasions by taking serial dilutions containing 0.4 to 3.4 units of hypertensinase. One series of tubes was incubated for four hours and the other for two. The

DETERMINATION OF HYPERTENSINASE 2 HOUR INCUBATION

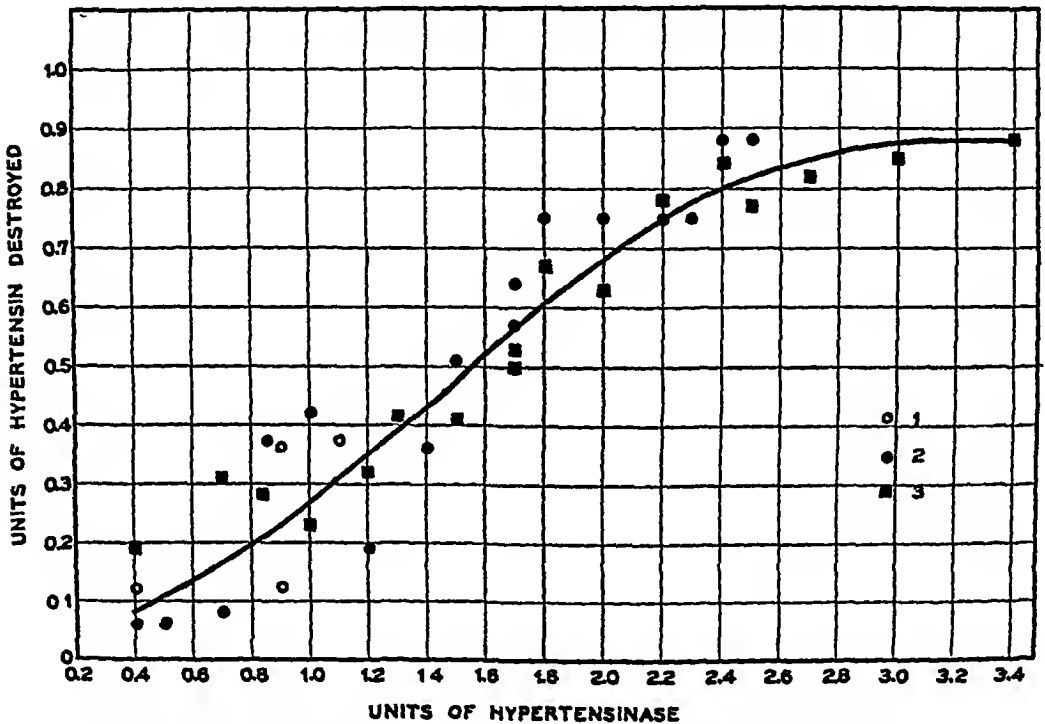


FIG 2 The destruction of hypertensin by hypertensinase during two hours of incubation at 37° C. Dots, circles, and squares represent experiments on different days

validity of the four hour curve of Fasciolo et al was confirmed (figure 1). From the number of units present as determined by the four hour incubation, and from the number of units of hypertensin destroyed by incubating for two hours, a two hour curve was constructed (figure 2). In this way, the same unit of hypertensinase as defined by Fasciolo et al has been retained and the time of incubation reduced to two hours.

Hypertensinase Content of Plasma The hypertensinase content of plasma of 10 normal dogs, four dogs nephrectomized 48 hours previously, and five dogs rendered hypertensive by constriction of the renal artery was determined. The results are shown in table 1. Normal values for hypertensinase lay between 1.5 and 3.9 units per c c of plasma. Similar values were found in the nephrectomized and hypertensive dogs.

TABLE I

The concentration of hypertensinase in the plasma of normal dogs, dogs nephrectomized 48 hours previously, and dogs made hypertensive by renal ischemia

Group	Dog No	Units of Hypertensinase per c c Plasma	Blood Pressure (mm Hg)
Normals	1	2.5	—
	2	2.8	—
	3	2.2	—
	4	2.4	—
	5	3.9	—
	6	2.4	—
	7	1.6	—
	8	2.1	—
	9	3.4	—
	10	2.2	—
Nephrectomized 48 hours previously	1	2.2	—
	2	1.2	—
	3	1.4	—
	4	2.2	—
Hypertensive by renal ischemia	1	1.9	260
	2	2.0	190
	3	1.9	160
	4	1.8	200
	5	2.4	190

SUMMARY AND CONCLUSIONS

1 Certain modifications have been introduced into the method of Fasciolo, Leloir, Muñoz, and Braun-Menendez⁵ for the determination of hypertensinase in plasma. The method is described in detail.

2 The plasma of normal dogs contains between 1.5 and 3.9 units of hypertensinase per cubic centimeter.

3 The hypertensinase content of plasma of dogs nephrectomized 48 hours previously and of dogs rendered hypertensive by renal ischemia is normal.

The author is indebted to Prof. B. A. Houssay and Dr. E. Braun-Menendez for their constant advice and suggestions and to Dr. L. F. Leloir and Dr. J. M. Muñoz for their preparation of the solution of hypertensin used in these experiments.

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THE SENSITIVITY TO HYPERTENSIN, ADRENALIN AND RENIN OF UNANESTHETIZED NORMAL, ADRENALECTOMIZED, HYPOPHYSECTOMIZED AND NEPHRECTOMIZED DOGS *

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IN 1898 Tigerstedt and Bergmann¹ discovered a pressor substance in normal kidneys to which they gave the name renin. This substance had a prolonged pressor effect when injected intravenously into animals, successive injections had a diminishing pressor action (tachyphylaxis), and it was not found in organs other than the kidneys. Their findings have been widely confirmed by subsequent investigators. With the development of a method of inducing hypertension experimentally in animals by Goldblatt, Lynch, Hanzal, and Summerville² and with the resultant evidence that this renal hypertension was apparently due to a humoral mechanism,^{3, 4} the rôle played by renin in experimental hypertension has recently been the subject of extensive study by many. Kohlstaedt, Helmer, and Page⁵ found that purified preparations of renin had no constrictor action when perfused in Ringer's solution through the vessels of an isolated rabbit's ear, but that when perfused with blood proteins ("reninactivator") a strong constrictor action was obtained. This has been confirmed by others^{6, 7}. Following a series of experiments by Houssay and his collaborators on the pressor and constrictor properties of venous blood of ischemic kidneys (recently reviewed by Houssay⁸), Braun-Menendez, Fasciolo, Leloir, and Muñoz^{9, 10, 11, 12} of the same laboratory in 1939 discovered a pressor substance, hypertensin, in the venous blood of ischemic kidneys. In its chemical, physical, and pharmacological properties it was identical with the pressor substance produced by the *in vitro* incubation of renin with blood globulins (hypertensin precursor, hypertensinogen). It differed in its properties from adrenalin, pitressin, tyramin, and urohypertensin. Hypertensin is rapidly destroyed by hypertensinase which is widely distributed throughout the body and which has no action on renin or on precursor^{9, 12}. Page and Helmer¹³ independently described the production of the same pressor substance which they called angiotonin, by the interaction of renin and blood colloids. The term "renin-activator" applied to the blood colloids seems inappropriate, however, since from the studies of Braun-Menendez et al^{9, 10, 14} it is apparent that renin is an enzyme and that the globulin fraction of the blood is the substrate on which it acts. Kohlstaedt and Page¹⁵ and Leloir, Muñoz, Fasciolo, and Braun-Menendez¹⁶ subsequently demonstrated the liberation of renin from the venous blood of

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perfused kidneys The relationship between renin and experimental renal hypertension, therefore, seems established

There is a considerable body of evidence indicating that there is a close relationship between the pituitary and adrenal glands and hypertension and that the normal kidney exerts a protective action against the development of experimental renal hypertension One of us (B A H⁸) has recently summarized the present knowledge of these relationships The purpose of this communication is to report a study made of the sensitivity to hypertensin, adrenalin, and renin of normal, adrenalectomized, hypophysectomized, and nephrectomized dogs in an attempt to clarify further the relationship which exists between these organs and renal hypertension

METHODS

Unanesthetized normal, adrenalectomized, hypophysectomized, and nephrectomized dogs weighing between 7 and 12 kilos were injected intravenously with 2 units of hypertensin, 10 gamma of adrenalin (Parke Davis) and 2 c c of a solution of hog renin in the order stated The blood pressure was recorded by a cannula in the femoral artery (novocaine being used as a local anesthetic) connected to a mercury manometer The animals were usually quiet during the experiment

Hypertensin was prepared according to the method of Muñoz, Braun-Menendez, Fasciolo, and Leloir¹¹, 0.18 c c contained 1 unit which is the amount as defined by Braun-Menendez, Fasciolo, Leloir, and Muñoz,¹⁷ which gives rise to an elevation of blood pressure of 25 to 30 mm Hg in a 10 kilogram chloralosed dog Renin was prepared from the cortex of hogs' kidneys according to the method of Braun-Menendez, Fasciolo, Leloir, and Muñoz⁹ and contained 1 unit in 0.025 c c The unit of renin as defined by Leloir, Muñoz, Braun-Menendez, and Fasciolo¹⁸ is the amount which when incubated at 37° C for two hours with an excess of precursor (6 to 8 c c of hypertensinase-free bovine plasma) is capable of forming 0.5 unit of hypertensin

Dogs were bilaterally nephrectomized under ether anesthesia by the lumbar or abdominal route The adrenals were removed in two stages at least two weeks apart using the lumbar approach After the removal of the second adrenal, 20 grams of sodium chloride alone or complemented in part with sodium citrate were administered daily by stomach tube The experiment was performed on the adrenalectomized and nephrectomized dogs 40 to 48 hours after operation All animals used showed definite symptomatic evidence of adrenal or renal insufficiency. Hypophysectomy was performed by the temporal approach, the animals being used one month to three years after the operation

Venous blood was withdrawn before adrenalectomy and again about 40 hours after adrenalectomy, some three to four hours before the dogs were injected with the pressor substances The indirect method of Leloir, Muñoz,

Braun-Menendez, and Fasciolo¹⁸ was used to determine the concentration of renin in the blood, and the method of Muñoz, Braun-Menendez, Fasciolo, and Leloir¹¹ was used to determine the concentration of precursor in the plasma.

RESULTS

The effect of the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c c of a solution of hog renin on the blood pressure of nine normal unanesthetized dogs, 12 dogs 40 to 48 hours after adrenalectomy, six hypophysectomized dogs, and nine dogs 40 to 48 hours after nephrectomy is summarized in table 1. The number of animals used was too small for statistical analysis.

1 Normal Dogs Following the intravenous injection of 2 units of hypertensin, the blood pressure rose on an average 35 ± 13 mm Hg with a range of 18 to 48, after 10 gamma of adrenalin, 30 ± 9 mm Hg with a range between 13 and 45, and after 2 c c of renin, 51 ± 15 mm Hg ranging between 30 and 78 mm. The upper limit of the normal response, therefore, was considered to be 48 mm Hg to hypertensin, 39 mm to adrenalin, and 66 mm to renin. In general, there was a parallelism in the blood pressure response to hypertensin and adrenalin. In only one dog (No 5) was the response to renin less than that to hypertensin. The duration of the pressor action of renin noted in four cases lasted on the average 37 minutes and in no instance exceeded one hour.

2 Adrenalectomized Dogs The initial blood pressure of the adrenalectomized dogs was considerably lower than in the normal controls, and all dogs were moderately weak and apathetic. Despite this, there was a normal or even increased sensitivity to hypertensin in all but one case (No 5) and to adrenalin a variable response with possibly a tendency to a slight decrease in sensitivity. The response to renin was variable. In dogs 2, 3, 4, 6, 9, and 10, the response to renin was normal and to hypertensin normal or above normal. In dogs 1, 7, 8, and 12, there was a normal or increased sensitivity to hypertensin, indicating a normal reactivity of the vessels, but a definitely diminished pressor response to renin in comparison with the pressor effect of hypertensin. Since the pressor action of renin is due to the hypertensin formed from its interaction with precursor,^{5,9} it seemed of importance to ascertain the concentration of precursor in the blood. It will be noted (table 2) that precursor was markedly reduced in the arterial blood approximately 40 hours after adrenalectomy as compared with values obtained before ablation of the second adrenal in dogs 7, 8, 11, and 12 in which the response to renin was decreased, and normal in dogs 9 and 10 in which the response to renin was normal. Dogs 5 and 11 were in frank insufficiency and shock and sensitivity to all three drugs was decreased. The duration of action of renin in these adrenalectomized dogs was usually shorter than in the controls. There was only a rough correlation between

TABLE I

The sensitivity of *unanesthetized* normal, adrenalectomized, hypophysectomized, and nephrectomized dogs to the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c c (80 units) of a solution of hog renin in the order stated

Group	Dog No	Wt	Initial Pressure	Elevation of Blood Pressure after			Duration of Action of Renin
				2 Units Hypertensin	10 Gamma Adrenalin	2 c c Renin	
Normal dogs		Kg	mm Hg	mm Hg	mm Hg	mm Hg	min
	1	8.5	135	45	41	78	—
	2	8.5	125	30	25	48	—
	3	8.6	150	40	30	65	—
	4	10.5	170	27	22	50	—
	5	9.0	180	40	28	33	—
	6	12.5	160	30	36	40	53
	7	8.5	200	40	35	65	45
	8	10.0	120	18	13	30	30
	9	8.5	130	48	45	48	19
Average Probable error				35 ±13	30 ±9	51 ±15	37 ±13
Adrenalectomized 48 hours previously	1	9.0	80	65	60	38	—
	2	8.0	98	52	40	65	—
	3	9.0	100	32	20	40	—
	4	11.0	130	35	12	45	45
	5	9.0	60	18	25	20	10
	6	9.0	70	50	25	40	10
	7	10.0	95	50	18	20	22
	8	10.0	75	37	20	28	23
	9	10.5	90	38	18	50	40
	10	10.0	25	40	16	40	25
	11	10.0	60	26	16	25	15
	12	8.5	60	50	36	40	9
Average Probable error				41 ±12	26 ±13	38 ±12	22 ±12
Hypophysectomized 1 month to 3 years previously	1	8.0	128	42	40	45	—
	2	9.0	140	44	44	50	—
	3	12.0	140	48	35	55	—
	4	8.0	130	30	30	40	—
	5	9.0	135	24	—5	30	—
	6	9.0	130	35	30	40	14
Average Probable error				37 ±8	29 ±16	43 ±8	—
Nephrectomized 48 hours previously	1	11.0	148	53	40	82	—
	2	11.0	135	52	25	80	—
	3	10.0	125	30	25	50	—
	4	10.5	180	30	25	60	180
	5	11.0	120	30	32	85	165
	6	9.0	130	65	55	120	60
	7	12.0	180	48	30	88	77
	8	12.5	160	22	10	38	38
	9	10.0	130	60	75	85	80
Average Probable error				43 ±15	35 ±18	77 ±23	100 ±53

the initial level of the blood pressure and the sensitivity to the pressor substances

3 Hypophysectomized Dogs The sensitivity of six unanesthetized hypophysectomized dogs to the injection of hypertensin, adrenalin, and renin appeared to be entirely normal (table 1)

4 Uremic Dogs Four out of nine of the dogs nephrectomized 40 to 48 hours previously (No 1, 2, 6, and 9) showed an increase in sensitivity to hypertensin, and three of these four dogs (No 1, 6, and 9) to adrenalin. The basic cause of the hyper-reactivity of the vessels to these drugs is not apparent. The same dogs (No 1, 2, 6, and 9) showed a greater increase in pressure than normal following the injection of renin, due at least in part to the hypersensitivity of the vessels to the hypertensin formed by the action

TABLE II

The concentration of precursor and renin in the plasma of unanesthetized dogs before and 48 hours after adrenalectomy

Dog No	Units of Precursor per c c		Units of Renin per c c	
	Before	After	Before	After
7	0.26	0.09	None	None
8	0.18	0.03	"	"
9	0.19	0.25	"	"
10	0.21	0.22	"	"
11	0.22	0.12	"	"
12	0.40	0.09	"	"

of renin on the precursor of the blood. In addition, two other dogs (No 5 and 7) showed an increase in sensitivity to renin. The pressor effect of renin was notably prolonged in four of five of the dogs in which it was determined.

5 Anesthetized Dogs Nephrectomized One to Three and One-Half Hours Previously The sensitivity to hypertensin, adrenalin, and renin was determined in nine dogs nephrectomized one to three and one-half hours previously. It was necessary to use chloralose anesthesia (10 c c of a 0.8 per cent solution per kilo intravenously) because of the restlessness of the animals so soon after operation. A control series consisted of nine normal chloralosed dogs whose kidneys were explored but not manipulated. The results are seen in table 3. Chloralose anesthesia did not diminish the sensitivity to hypertensin, adrenalin, or renin, nor was the duration of the pressor action of renin altered. In the recently nephrectomized animals there was no increase in sensitivity to either hypertensin or adrenalin, nor in the majority of the animals to renin. In three (No 3, 7, and 8), however, the pressor response to the injection of renin was decidedly greater than normal, and in two (No 2 and 8) the pressor effect lasted two and two and a quarter hours respectively. In two dogs (No 8 and 9), the amount of precursor in the blood before and three hours after operation was unchanged.

DISCUSSION

The observations on adrenalectomized dogs indicate that the vessels reacted normally or almost normally in response to injections of hypertensin and adrenalin until the advent of terminal shock. The sensitivity to injections of renin was normal in six cases and reduced in six cases, which is in accord with the observations of Williams, Diaz, Burch, and Harrison¹⁹ and of Friedman, Somkin, and Oppenheimer²⁰. Remington, Collings, Hays, and Swingle²¹ noted a normal response of adrenalectomized dogs to large

TABLE III

The sensitivity of *chloralosed* normal and recently nephrectomized dogs to the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c c (80 units) of a solution of hog renin in the order stated

Group	Dog No	Wt	Initial Pressure	Elevation of Blood Pressure after			Duration of Action of Renin
				2 Units Hypertensin	10 Gamma Adrenalin	2 c c Renin	
Normal dogs 1 to 5 hours after exploration of kidneys		Kg	mm Hg	mm Hg	mm Hg	mm Hg	min
	1	10 0	130	25	32	20	10
	2	9 0	150	40	66	60	27
	3	8 0	165	25	30	40	10
	4	9 0	170	36	10	60	10
	5	9 0	105	50	24	40	30
	6	7 0	160	48	40	40	30
	7	9 0	140	44	30	20	40
	8	9 0	120	62	66	40	20
	9	11 0	160	35	16	45	60
	Average Probable error			41 ±11	35 ±19	41 ±13	26 ±16
Nephrectomized 1 to 3½ hours previously	1	12 5	130	48	50	55	24
	2	13 0	130	30	45	60	120
	3	12 0	120	36	34	70	58
	4	11 0	130	50	36	44	33
	5	7 0	140	28	82	40	43
	6	10 5	170	27	40	40	26
	7	10 5	130	62	43	75	28
	8	8 5	110	64	57	78	135
	9	13 5	120	58	52	43	43
	Average Probable error			45 ±14	49 ±13	56 ±14	56 ±39

doses of renin but a diminished response to small doses beginning almost immediately after the withdrawal of cortical extract. The dose used by us may have been too large to detect the early appearance of diminished sensitivity. In four cases there was a normal response to hypertensin but a diminished response to renin. In these cases the reactivity of the vessels may be considered normal. In these same cases, but not in two others in which the sensitivity to hypertensin and renin was normal, the concentration of precursor in the plasma was found to be distinctly reduced, which probably is a factor not only in the diminished pressor response to renin, but also in

the short duration of its action, since Leloir, Muñoz, Braun-Menendez, and Fasciolo¹⁸ have shown that the amount of hypertensin formed by the action of a given amount of renin depends upon the amount of precursor present. In two dogs in which the pressor response to renin was normal the concentration of precursor in the plasma was found to be normal. These studies give no clue as to the cause of the diminution in the concentration of precursor. No renin was found in the blood of any of the dogs 40 to 48 hours after adrenalectomy by the indirect method of Leloir, Muñoz, Braun-Menendez and Fasciolo,¹⁸ which is capable of detecting 0.2 unit of renin or even less with accuracy. Although the possibility still exists despite this negative finding, it seems unlikely that the cause of the reduction of precursor was the liberation of renin by the kidney such as occurs in certain shock-like conditions.²²

When the adrenalectomized animals were in profound shock, such as dogs 5 and 11 and several others not included in this series, the sensitivity to hypertensin and renin was uniformly depressed, and that to adrenalin variable. Elliot²³ reported a marked pressor response to large doses of adrenalin in cats in terminal adrenal insufficiency. Armstrong, Cleghorn, Fowler, and McVicar²⁴ likewise observed in cats in adrenal insufficiency a good pressor effect from the injection of adrenalin in doses similar to those used by us.

It seems plausible to assume that following adrenalectomy two factors are involved in the diminished sensitivity to injections of renin. First, at a late stage of adrenal insufficiency, the vessels lose their normal reactivity not only to renin but to hypertensin and at a later stage to adrenalin as well. Second, in certain animals but not in all (four of six of the dogs tested in this series) there is a clear reduction in the concentration of precursor in the blood so that the amount of hypertensin capable of being formed by the renin injected is reduced. Whether this factor plays a rôle in the fall of blood pressure of hypertensive animals after adrenalectomy can only be surmised at this time.

In the hypophysectomized animals no alteration from normal was noted in the sensitivity to hypertensin, adrenalin, or renin. Williams, Diaz, Burch, and Harrison¹⁹ observed an increased sensitivity to renin in hypophysectomized rats. We are unable to explain the difference in our results. It is probable, however, that such factors as species variations and anesthesia account for the differences, or, as the authors suggest, the lower initial pressure of the rats after hypophysectomy. The initial pressure of our dogs was normal. Our results throw no light on the dampening effect of hypophysectomy on hypertension from renal ischemia.

Recently nephrectomized (one to three and one-half hours) dogs reacted normally to injections of hypertensin, adrenalin, and, in the majority of instances, to injections of renin. In three instances, however, the pressor action of renin was greater and in two it lasted much longer than in normal dogs. Forty-eight hours after nephrectomy distinct differences were ob-

served in that several dogs showed a clear increase in sensitivity to hypertensin and to adrenalin. There was likewise an increase above normal in the pressor response to renin in the majority of the dogs, which is in accord with the observations of other investigators^{1, 25, 26, 27, 28, 29}. The duration of the pressor action of renin was more than twice as long as in the normal control dogs. At least three factors appear to account for the hypersensitivity to and the prolonged action of renin in the uremic dogs: (a) The vessels of the dogs 48 hours after nephrectomy are more sensitive than normal to the injection of the pressor substances used. (b) Given enough time, the amount of hypertensin formed by a given amount of renin depends upon the concentration of precursor present. Muñoz, Braun-Menendez, Fasciolo, and Leloir¹¹ demonstrated that 48 hours after nephrectomy the concentration of precursor is increased. Therefore, in these dogs the increase in the concentration of precursor undoubtedly plays a rôle in the heightened and prolonged pressor effect of renin. (c) It has been shown by Houssay, Braun-Menendez, and Dexter²² that in dogs nephrectomized 48 hours previously renin after its injection intravenously persists in detectable amounts in the blood for two to three hours or more, whereas in normal dogs it disappears usually within an hour. The velocity of the reaction between renin and precursor to form hypertensin depends on the concentration of renin present¹⁸. Since renin persists for a longer time in the blood of these animals, the rate at which hypertensin forms is increased, thereby playing a part in the increased height to which the blood pressure rises as well as to the prolongation of the pressor action.

SUMMARY

1 The sensitivity of unanesthetized normal, adrenalectomized, and nephrectomized (uremic) dogs to 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. of a solution of hog renin has been determined.

2 Forty-eight hours after bilateral adrenalectomy, the sensitivity to hypertensin and adrenalin was usually normal unless terminal shock appeared. The sensitivity to renin was sometimes normal and sometimes reduced. The decrease in the sensitivity to renin at a time when the vessels were reacting normally to hypertensin was associated in four instances with a fall in the concentration of hypertensin precursor (hypertensinogen) in the plasma.

3 Dogs hypophysectomized one month to three years previously reacted normally to the injection of hypertensin, adrenalin, and renin.

4 Chloralosed dogs recently nephrectomized reacted normally to hypertensin and adrenalin and usually to renin. In three of nine dogs the pressor effect of renin was greater, and in two of nine it lasted distinctly longer than in the normal controls.

5 Unanesthetized dogs nephrectomized 48 hours previously frequently were hypersensitive to hypertensin, adrenalin, and renin. The duration of action of renin was usually markedly prolonged. The causes of the hypersensitivity to renin in these dogs are discussed.

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THE DESTRUCTION AND ELIMINATION OF RENIN IN THE DOG *

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TIGERSTEDT and Bergmann¹ described a pressor substance, renin, which is found in kidney but not in other organs and which has a prolonged pressor effect when injected intravenously. Kohlstaedt and Page² showed that purified renin had no vasoconstrictor action when perfused through a rabbit's ear but that it became active when mixed with blood colloids. This has been corroborated by others.³ Braun-Menendez, Fasciolo, Leloir, and Muñoz^{4, 5, 3} identified a pressor and vasoconstrictor substance, which they called hypertensin, in the venous blood of ischemic kidneys and showed that the same substance could be obtained in vitro by incubation of renin with blood globulins. This was confirmed independently by Page and Helmer⁶ who have called the pressor substance "angiotonin" and the blood globulins "renin-activator."

According to Muñoz, Braun-Menendez, Fasciolo, and Leloir,⁷ the mechanism of renal hypertension might be summarized as follows. Renal ischemia determines the secretion of renin^{8, 9}. This protein is an enzyme which acts on a blood globulin (hypertensin precursor) and gives rise to a substance (hypertensin) which produces vasoconstriction. Another enzyme "hypertensinase" which destroys hypertensin is present in blood and tissues.

Because of the important rôle played by renin in the development of experimental hypertension, a study has been made of the mechanisms by which renin is eliminated or destroyed by the body. Three general methods of investigation have been utilized: (a) search for renin in the urine after its intravenous injection, (b) study of the disappearance of renin from the blood after its injection into normal animals and animals deprived of certain organs, and (c) search for a substance in blood which would neutralize or destroy renin.

METHODS

Hog renin was prepared according to the method of Braun-Menendez, Fasciolo, Leloir, and Muñoz³ and contained approximately 100 units per c c, one unit of renin being the amount which when incubated for two hours at 37° C with hypertensinase-free precursor is capable of giving rise to the formation of 0.5 unit of hypertensin¹⁰. The renin content of plasma was determined by the direct method of Leloir, Muñoz, Braun-Menendez, and Fasciolo¹⁰.

The renin content of urine was determined in most instances using the same method as for plasma. In a few instances urine was previously ex-

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tracted for renin by acidifying to pH 4.5, adding ammonium sulphate (400 gm per liter), filtering, dialyzing the precipitate in a cellophane sac overnight in the icebox, redissolving the contents of the sac in distilled water, neutralizing and filtering. This method of extraction was tested by adding renin to urine. Little or no apparent loss of renin occurred by the process of extraction.

In the determination of renin in the urine by the method used, which consists in the incubation for two hours at 37° C of variable amounts of urine with an excess of hypertensinase-free precursor, two causes of error may exist. Another pressor substance may exist in the urine or the pressor

TABLE I

Excretion of renin in the urine after the intravenous injection of variable amounts of renin into normal anesthetized or unanesthetized dogs

Dog	Wt	Anesthesia	Amount of Renin Injected (1 cc 100 U)	Diuresis		Renin in Urine		Renin Recovered
				Volume	Hours of Observation	Presence	Amount in Units	
	kg		cc	cc				%
1	15	None	2	4	1	No	—	—
2	10	Chlor	2	?	1	No	—	—
3	12	None	2	?	1	No	—	—
4	13	None	2	150	2	No	—	—
5	17	None	2	57	1.5	Traces	—	—
6	18	None	2	18	1.5	No	—	—
7	16	Amytal	3	13	1.5	Yes	18	6
8	15	Chlor	4	143	2	Yes	34	8.5
9	12	None	4	57	1	Yes	?	?
10	13	Chlor	5	103	2	Yes	36	7.2
11	14	None	5	148	2	Yes	140	28
12	14	None	10	76	1.5	Yes	?	?
13	13	None	10	28	2	Yes	420	42

substance formed by incubation of urine and precursor may not be hypertensin. If a control tube prepared by mixing urine and precursor without incubating gave no pressor response, no extraneous pressor substance existed in the urine. On the other hand, the pressor substance formed was identified as hypertensin if it was destroyed by incubation with hypertensinase prepared from red cells or liver.¹¹

Dogs were used in all experiments. Nephrectomy was performed by the lumbar or abdominal approach using ether or chloralose (10 cc of a 0.8 per cent solution per kilo intravenously) as an anesthetic. Hepatectomy was performed on chloralosed dogs by making an Eck fistula by means of a Payr's tube between the portal vein and left renal vein, both kidneys being removed, or by tying the hepatic artery and ligating one by one the lobes of the liver. With this technic, hepatectomy is practically complete and studies from this Institute show that no hepatic function remains. Evisceration was performed on chloralosed dogs by removal of all abdominal viscera with the exception of the liver, the lobes of which were ligated. After hepatectomy

TABLE II

Concentration of renin in blood after the injection of 2 c c (80 units) of hog renin intravenously into *unanesthetized* normal, recently nephrectomized and uremic dogs

Group	Dog	Wt	Units of Hypertensin in 8 c c of Plasma					
			Before	After				
				5 min	30 min	60 min	120 min	180 min
Normals	1	14.0	None	0.64	0.04	0.08	None	None
	2	8.0	None	0.48	0.09	0.09	None	None
	3	9.0	None	0.75	None	None	None	None
	4	9.0	None	1.89	None	None	None	None
	5	9.0	None	0.39	None	None	None	None
	6	11.0	None	1.14	0.18	None	None	None
Nephrectomized 3 to 4 hours previously	1	9.0	None		0.80	0.12	None	None
	2	14.5	None		0.18	0.06	None	None
	3	14.0	None	0.82	0.50	0.08	None	None
	4	11.5	None	0.53	0.29	None	None	None
Nephrectomized 48 hours previously	1	10.5	None		0.23	0.36	0.21	0.21
	2	12.0	None		0.36	0.24	0.15	0.11
	3	9.0	None			0.33	0.20	0.13
	4	12.5	None		1.01	0.42	0.22	0.03
	5	12.5	None		0.38	0.09	0.19	None
	6	10.0	None		1.36	0.30	0.08	None
	7	14.0	None		1.29	0.62	0.45	0.13
	8	14.5	None		0.82	0.20	0.18	0.16

(Results expressed as units of hypertensin formed after two hours incubation at 37° C with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

and evisceration, a direct transfusion from another chloralosed dog was given before injecting renin.

In transfusing recently nephrectomized dogs with uremic blood and uremic dogs with normal blood, the chloralosed recipient dog was placed on a scale and bled half of his calculated blood volume. The blood volume was assumed to be 7 per cent of the body weight. Transfusion from the donor dog, also anesthetized with chloralose, was made by means of a short rubber tube between the carotid artery of the donor and the jugular vein of the recipient. Enough blood was transfused to restore the original weight of the recipient. Two or three such bleedings and transfusions were thus performed, so that at the end of the third 87.5 per cent of the blood of the recipient was calculated to be donor blood.

For the perfusion of isolated organs, either the heart-lung preparation of Starling or an artificial pumping system was used. The heart-lung preparation of dogs was made in the classical manner. The defibrinated blood was allowed to circulate for approximately one hour or more before beginning the perfusion of the isolated organ in order to eliminate the vasoconstrictor substance (Spatgift) which is present in defibrinated blood.

For perfusion of the liver, the hepatic artery was cannulated and received blood from the arterial side of the circuit. The portal vein received blood from the circuit distal to the peripheral resistance. Kidneys were perfused by two methods, one with the heart-lung preparation and the other with a system of Dale-Schuster pumps and a Hooker oxygenator. In the latter, defibrinated blood which had circulated through the heart-lung preparation for an hour or more was used.

RESULTS

The Excretion of Renin in the Urine By means of a catheter introduced in the urinary bladder, urine was collected before and at half hour intervals after injection of variable amounts of renin into the jugular vein of unanesthetized or anesthetized dogs (table 1). In six experiments 2 cc of renin were injected and in only one could traces of renin be recognized in the

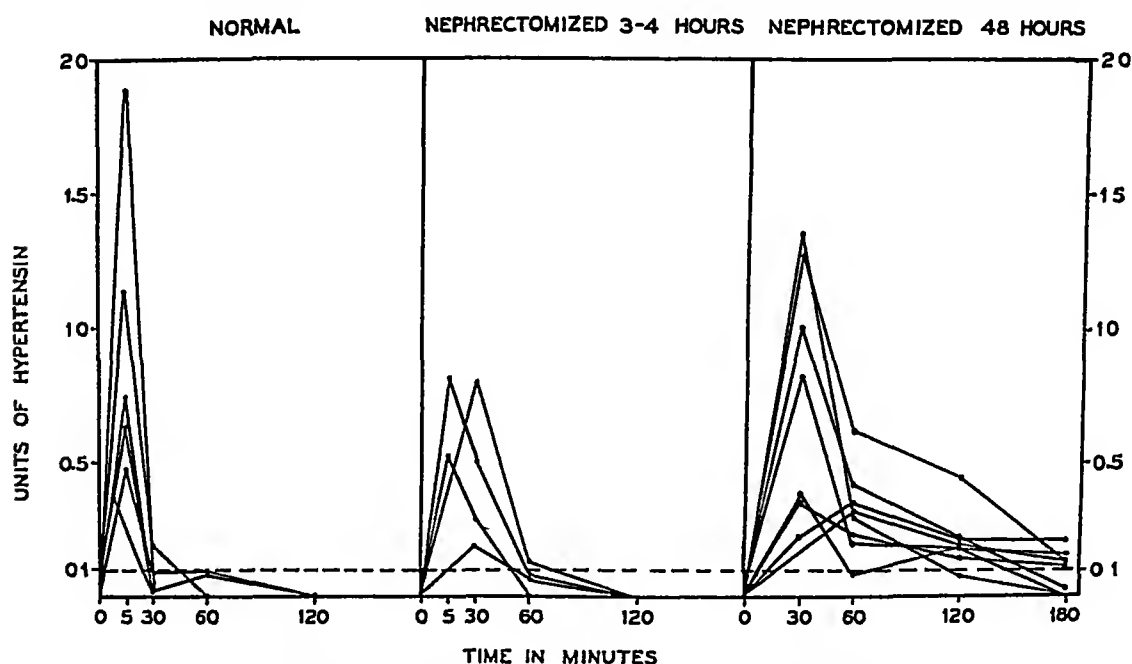


FIG 1 Concentration of renin in blood after the injection of 2 cc (80 units) of hog renin intravenously into unanesthetized normal, recently nephrectomized, and uremic dogs

(Results expressed as units of hypertensin formed after two hours incubation at 37° C with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

urine. The injection of greater amounts was followed in every instance by the renal excretion of renin. The amount of renin recovered from the urine was from 6 to 42 per cent, being roughly proportional to the amount injected. The second half hour sample of urine contained most of the renin excreted and none was present two hours after the injection. These results have been reported elsewhere.¹²

The Disappearance of Injected Renin from the Blood of Unanesthetized Normal and Nephrectomized Dogs Two cc of renin were injected into

TABLE III

Concentration of renin in blood after the intravenous injection of hog renin into chloralosed normal, recently nephrectomized, nephrectomized and hepatectomized, eviscerated, and uremic dogs

(Results expressed as units of hypertensin formed after two hours incubation at 37° C with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

Group	Dog	Wt	Amount of Renin Injected	Volume of Plasma Used in Testing	Units of Hypertensin in Plasma							
					Before	After						
						5 min	15 min	30 min	60 min	120 min	180 min	300 min
Normal intact dogs	1	kg	cc	cc	None		0.80	0.21	None			
	2	15.0	4.0	6.0	None		0.60	0.08	0.04			
	3	13.0	5.0	6.0	None		1.30	0.26	None			
	4	15.0	2.0	6.0	None	0.57		0.10	0.04			
	5	15.0	2.0	6.0	None	0.73		None				
Normals, kidneys explored	1	11.5	2.0	8.0	None			0.48	0.26	0.10	0.04	
	2	10.0	2.0	8.0	None	1.97	1.45		0.30	None	0.16	
	3	8.0	2.0	8.0	None	0.82	0.70	0.64	None	0.45	0.66	
	4	9.0	2.0	8.0	None	0.54	0.74	1.23	0.52	0.33	None	
Nephrectomized 1 to 3 hrs previously	1	13.0	2.0	8.0	None			0.69		0.12	None	
	2	9.0	2.0	8.0	None			0.71	0.59	0.26	None	
	3	11.0	2.0	8.0	None			0.80	0.27	None	None	
	4	7.0	2.0	8.0	None			0.31	0.09	None	None	
Nephrectomized and hepatectomized	1	16.0	2.0	8.0	None	0.42			0.49	0.09	0.07	
	2	18.0	4.0	4.0	None	0.85		0.56	0.58	0.10	0.02	
Eviscerated	1	20.0	3.0	4.0	None	1.00			0.43	0.24	0.03	
	2	23.0	3.0	6.0	None	0.66			0.50	0.36	0.13	
Nephrectomized 48 hrs previously	1	7.0	3.0	6.0	None	2.68			1.12	0.41	0.41	0.38
	2	7.5	3.0	6.0	None	2.26			0.24	0.16	0.14	0.07
	3	7.0	3.0	6.0	None	1.85			0.36	0.19	0.19	0.11

the jugular vein of six control dogs whose kidneys were explored but not manipulated three or four hours previously under ether anesthesia, four dogs nephrectomized three or four hours previously, and eight dogs nephrectomized 48 hours previously. The results are shown in table 2 and figure 1. Renin usually disappeared from the blood stream in less than 30 minutes in the control group, in about an hour in the recently nephrectomized dogs, and small but definite amounts persisted for two to three hours in the majority of the dogs nephrectomized 48 hours previously. Differences in the amount of renin present in the first 15 or 30 minutes are not significant and are attributable to inadequate amounts of precursor used in incubating with the blood samples containing such large quantities of renin. These experiments indicate that in nephrectomized dogs there is a delay in the disappearance of the injected renin, especially marked if nephrectomy is per-

formed 48 hours previously. Because of obvious difficulties in working with unanesthetized animals, the problem was pursued using chloralosed dogs.

*The Disappearance of Injected Renin from the Blood of Anesthetized Normal, Nephrectomized, Hepatectomized and Eviscerated Dogs** In this group of experiments all animals were anesthetized with chloralose (10 cc of a 0.8 per cent solution per kilo) intravenously. Renin was injected as in

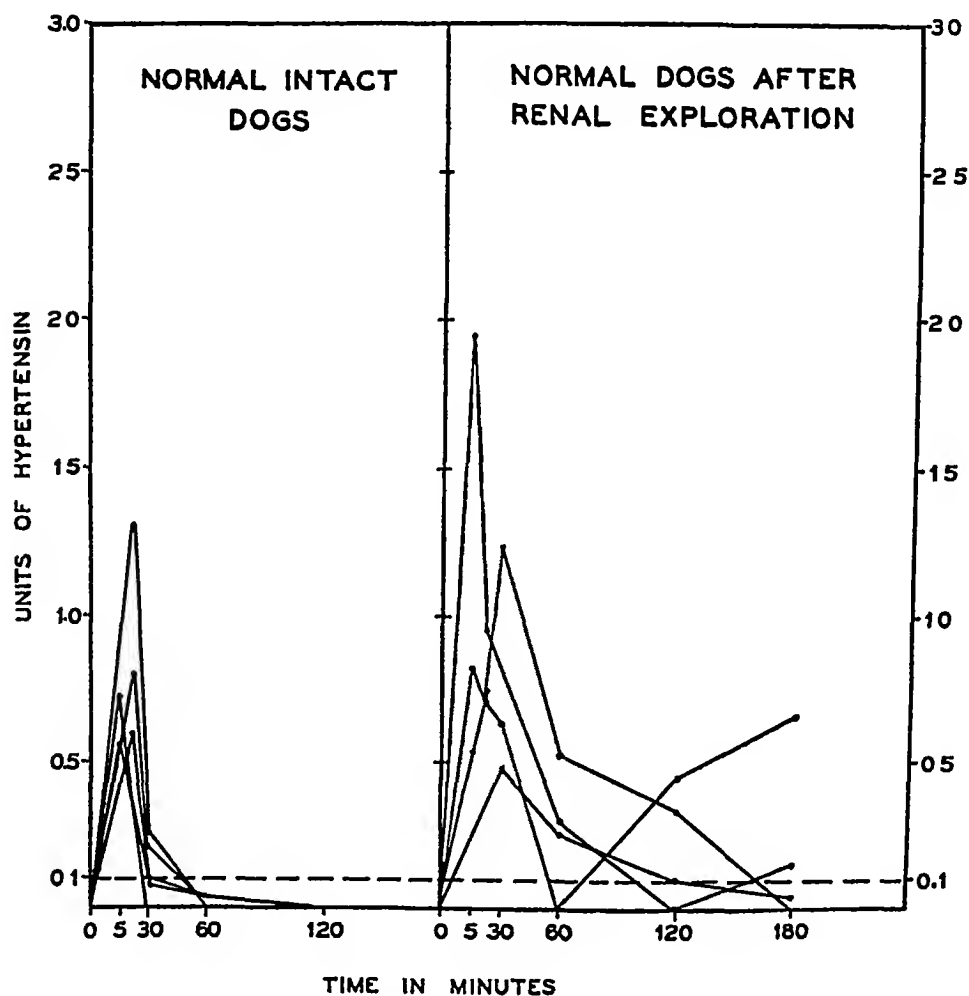


FIG 2 Concentration of renin in blood after the intravenous injection of hog renin into normal chloralosed dogs and chloralosed dogs whose kidneys had been explored but not manipulated

(Results expressed as units of hypertensin formed after two hours incubation at 37° C with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

the preceding experiments to five control intact dogs, four dogs whose kidneys were explored but not manipulated, four dogs nephrectomized one to three hours previously, three dogs nephrectomized 48 hours previously, two dogs hepatectomized and nephrectomized immediately before the injection of renin, and two dogs eviscerated immediately before the injection of renin. The results are shown in table 3 and figures 2 and 3.

In anesthetized intact dogs renin disappeared from the blood in about 30 minutes but great irregularities were observed in the disappearance of renin from the blood of the anesthetized dogs whose kidneys were explored. In two instances there were actual increases in the concentration of renin which were far beyond the error of the method. Such increases were never observed in any of the nephrectomized animals. One of these dogs (No 3) presented the picture of shock with low blood pressure and sighing respira-

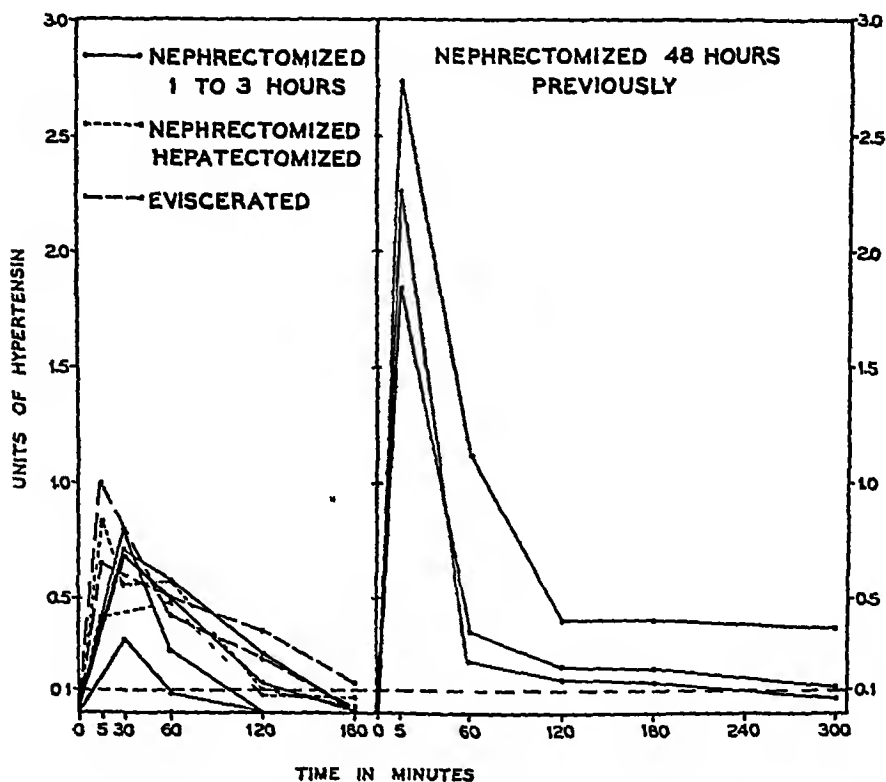


FIG 3 Concentration of renin in blood after the intravenous injection of hog renin into chloralosed recently nephrectomized, nephrectomized and hepatectomized, eviscerated, and uremic dogs

(Results expressed as units of hypertensin formed after two hours of incubation at 37° C with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

tions. The other (No 4), however, appeared in good condition. Both dogs 1 and 2 had low pressures without showing increased amounts of renin in the blood. The striking difference in the disappearance of renin from the blood of this group of dogs and the normal anesthetized or unanesthetized dogs is presumably a consequence of the operation under chloralose anesthesia leading to impaired renal function or shock, and manifested by the production of renin or by its faulty destruction or elimination.

In dogs nephrectomized one to three hours previously, renin disappeared from the blood before the second hour, and in those nephrectomized 48

hours previously between three and four hours or more. As compared with the disappearance curves in the unanesthetized dogs, there was a slight delay in the disappearance of renin from the blood of chloralosed dogs. Immediately after nephrectomy and hepatectomy, and immediately after evisceration, renin disappeared at the same rate as in the dogs recently nephrectomized (table 3 and figure 3).

From these experiments it may be concluded that under certain circumstances the kidney may produce renin in sufficient amounts to be detected in the blood by the method employed, that chloralose anesthesia delays somewhat the time of disappearance of injected renin from the blood but that mechanisms other than those exerted directly by the kidneys, liver and other abdominal viscera are of importance in the destruction of renin by the body. Indeed renin disappears rapidly from the blood in eviscerated and in recently nephrectomized dogs. The rate of disappearance is slightly but definitely prolonged when compared with that of the intact control dogs. On the other hand, in the uremic anesthetized and unanesthetized dogs there is a great delay in the disappearance of injected renin. Two possibilities present themselves to explain the fact that the ability of the body to destroy renin is much reduced in dogs nephrectomized 48 hours previously and only slightly reduced in recently nephrectomized or eviscerated dogs: (a) that the normal kidney secretes a substance which neutralizes or destroys renin or its action and that this substance persists in the blood for some hours after nephrectomy; (b) that renin is destroyed by the tissues of the body but that in uremia there is a disturbance of this metabolic activity on the part of the tissues. The following experiments were devised to investigate these possibilities.

Attempts to Demonstrate the Ability of Blood Withdrawn from Various Sites to Destroy or Inhibit the Action of Renin. Hog renin (0.25 c.c.) was added to 80 c.c. of citrated blood obtained from the carotid artery of a chloralosed dog. Merthiolate (3.5 c.c.) was added to prevent bacterial growth. The blood was incubated for three hours at 37° C. Samples of blood were withdrawn at five minutes, one hour, two hours, and three hours and their renin content estimated. There was no diminution in the amount of renin present in any of the samples, thereby indicating that renin was not adsorbed to red cells or destroyed by contact with whole blood during this interval.

By the method described, no destruction of renin or of its action by plasma or whole blood from the jugular vein, carotid artery, suprahepatic vein, and renal vein of a normal etherized dog could be detected. Similarly negative results were obtained with serum obtained from the hepatic veins of two livers after perfusion with the heart-lung preparation for 28 and 42 minutes respectively and from the venous blood of four kidneys perfused 40, 113, 35, and 60 minutes respectively. No destructive action on renin could be demonstrated by whole defibrinated blood obtained from the renal vein

of one kidney perfused for 30 minutes. The amount of renin in whole blood, plasma, or serum after two hours of incubation was exactly the same as in the sample withdrawn immediately after the addition of renin.

The Disappearance of Injected Renin from the Blood of a Recently Nephrectomized Dog Transfused with Uremic Blood and from the Blood of a Uremic Dog Transfused with Normal Blood In order to ascertain if the slow disappearance of renin from the blood of dogs 48 hours after nephrectomy was due to an alteration in the normal metabolic destruction of renin by the tissues or the absence of some neutralizing or destructive

TABLE IV

Concentration of renin in blood after the injection of 3 c.c. (120 units) of hog renin intravenously into uremic dogs transfused with normal blood and recently nephrectomized dogs transfused with uremic blood.

(Results expressed as units of hypertensin formed after two hours incubation at 37° C with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

Group	Dog	Wt	Calculated Amount of Circulating Donor Blood	Units of Hypertensin in 6 c c of Plasma						Condition Symptomatically
				Before	After					
					5 min	1 hour	2 hours	3 hours	5 hours	
Uremic dogs with normal blood	1	kg	%	None	1 56	0 56	0 56	0 51	0 46	Severe uremia
	2	7 0	87 5	None	1 36	0 53	0 34	0 23	0 05	Mod uremia
	3	8 0	87 5	None	1 26	0 19	0 09	0 12	None	Mild uremia
Recently nephrectomized dogs with uremic blood	1	8 0	75 0	None	1 52	0 52	0 08	0 05	None	Good
	2	7.3	87 5	None	2 26	1 11	0 25	0 09	0 02	Good
	3	6 5	75 0	None	1 37	0 28	None	None	None	Good

factor present in normal blood, the blood of three normal dogs nephrectomized 48 hours previously was transfused into three normal dogs nephrectomized a few minutes previously, and the blood of three normal dogs was transfused into three dogs nephrectomized 48 hours previously. By the method described the recently nephrectomized dogs were calculated to have approximately 75, 75, and 87.5 per cent uremic blood respectively, and the uremic dogs 87.5 per cent each of normal blood. Three c.c. of renin were injected intravenously into each and its rate of disappearance noted for five hours (table 4 and figure 4). Renin disappeared from the blood of uremic dogs with normal blood in three to five hours or more, the time of disappearance seemingly being influenced by the severity of the uremia, and from the blood of recently nephrectomized dogs with uremic blood in less than three hours in each case. It has been concluded, therefore, that the marked

interference with the normal destruction of renin in the uremic dog is due to a disturbance of the destructive action of the tissues in uremia rather than to the absence of some substance which is present in the blood of recently nephrectomized dogs and which disappears 48 hours after nephrectomy

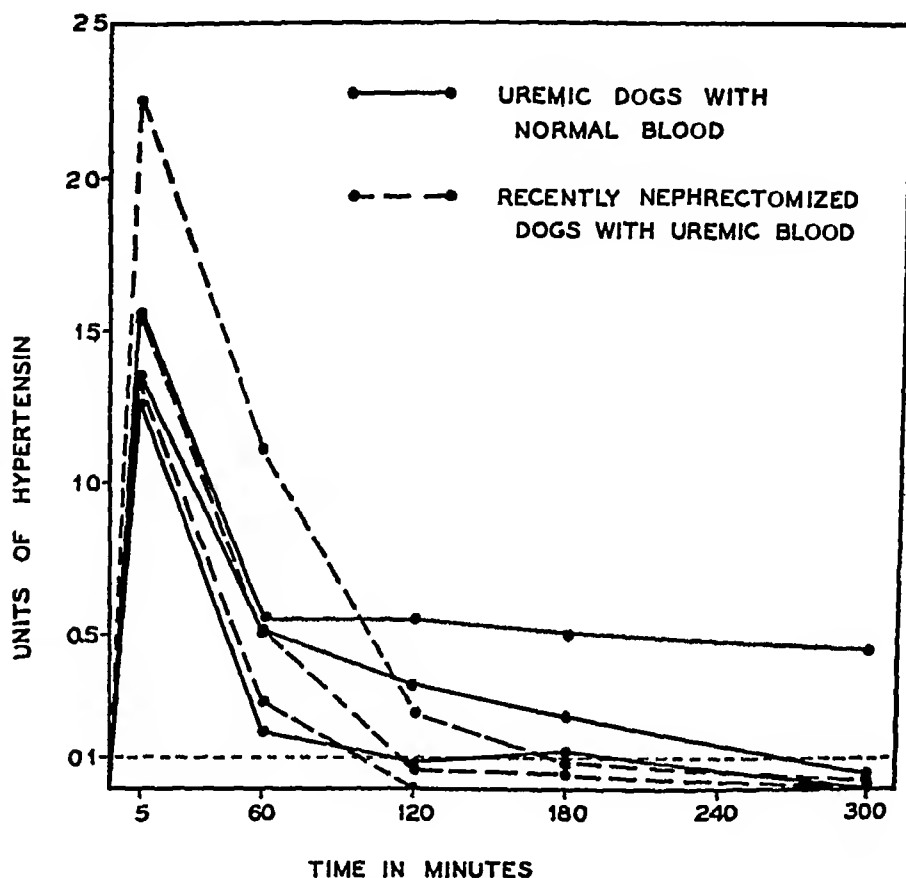


FIG 4 Concentration of renin in blood after the injection of 3 cc (120 units) of hog renin intravenously into uremic dogs transfused with normal blood and recently nephrectomized dogs transfused with uremic blood.

(Results expressed as units of hypertensin formed after two hours incubation at 37° C with precursor. The method of assay is considered accurate to within 0.1 unit of hypertensin. Values of less than 0.1 unit have, therefore, been considered to be negative.)

DISCUSSION

Considerable evidence exists in the literature that the kidney has a protective action against the renal humoral substance responsible for hypertension from renal ischemia. For a summary of the literature and review of the work done in this Institute, see Fasciolo^{13, 14, 15} and Houssay¹⁶. This protective action is usually not sufficient to prevent the development of hypertension by constricting the renal artery of the opposite kidney, but under certain conditions of stress, the influence of the normal kidney becomes manifest. It is of interest to consider the evidence in the light of the present investigation.

Our observations show that in normal unanesthetized dogs whose kidneys were explored three to four hours previously under ether anesthesia, renin disappeared from the blood stream in less than 30 minutes. In recently nephrectomized dogs it disappeared in about an hour (see table 2 and figure 1). Anesthesia with chloralose delayed somewhat the disappearance of renin, but the same difference existed between normal unoperated dogs and dogs recently nephrectomized. In the former renin disappeared in about 30 minutes, in the latter before the second hour (see table 3 and figure 2). Dogs whose kidneys were explored form a group apart which we shall consider presently. These results indicate that the kidneys play a rôle in the destruction of renin in the body.

The excretion of renin in the urine does not explain the greater rapidity with which renin disappeared from the blood of normal dogs because renin appeared in the urine only when amounts greater than 2 c c were injected (table 1). Our observations lend no support to the hypothesis that the normal kidney secretes a substance which neutralizes or destroys renin. We were not able to demonstrate the ability of blood withdrawn from various sites to destroy or inhibit the action of renin, nor did the transfusion of normal blood restore the ability of uremic dogs to destroy renin. Perhaps the kidney metabolizes or neutralizes renin but direct proofs of this action have not yet been given.

Of all the abdominal organs the kidneys are the most active in the destruction of renin because hepatectomized and nephrectomized dogs and eviscerated dogs behave like recently nephrectomized dogs after the injection of renin (figure 3). It is evident, however, that the kidney is not the principal factor in the destruction of renin in the body because this substance disappears from the blood in about one to two hours after its injection into recently nephrectomized dogs. Mechanisms other than those exerted directly by the kidneys, liver, and other abdominal viscera are of importance in the destruction of renin by the body. This destructive action of the tissues is disturbed in uremia as shown by the persistence for three to five hours of small amounts of renin in the blood of dogs nephrectomized 48 hours previously. The more rapid disappearance of renin in normal, recently nephrectomized and eviscerated animals as compared with uremic dogs is not due to the persistence in the blood of some substance neutralizing or destroying renin. This was indicated by studying the rate of disappearance of renin from the blood of uremic animals with approximately 87.5 per cent of normal blood and from recently nephrectomized animals with approximately 75 to 87.5 per cent of uremic blood. Renin disappeared slowly from the uremic dogs with normal blood and rapidly from the recently nephrectomized dogs with uremic blood. Furthermore, no destructive action against renin could be demonstrated *in vitro* of blood, serum, or plasma obtained from hepatic veins, renal vein, jugular vein, or carotid artery.

Exactly what the bodily mechanisms for the destruction of renin are, outside of its elimination in the urine, we are unable to state. The circulating blood has no apparent destructive action. The abdominal viscera apart from the kidney do not appear to play an important rôle in its destruction. Preliminary and incomplete experiments on the disappearance of renin from a perfusing system of isolated organs including the kidney, liver and muscles (leg) have as yet yielded no information as to the tissue or tissues concerned in its destruction or the manner in which such destruction takes place.

As to the four dogs anesthetized with chloralose whose kidneys were explored, they cannot be considered as normal controls. In two of them, the blood pressure was very low and one presented the picture of shock. The delayed disappearance of renin in this group may be explained by the production of renin by the kidney and possibly also by an inhibition of renal function due to the abnormal conditions created by the chloralose anesthesia and the abdominal operation. This is supported by the observation of dog 3 in which the concentration of renin in the blood actually increased (table 3 and figure 2). The secretion of renin by the kidney in shock may be a mechanism by which the body tends to restore the lowered blood pressure in this condition.

SUMMARY AND CONCLUSIONS

1 A study has been made of the mechanism by which renin injected intravenously disappears from the blood.

2 After the intravenous injection of 2 to 3 c.c. of a solution of hog renin into normal dogs, it disappears from the blood usually within 30 minutes.

3 After the intravenous injection of the same amount of renin into dogs recently nephrectomized, renin disappears from the blood in one to three hours. The same delay is observed in nephrectomized and hepatectomized and in eviscerated dogs. The kidneys seem then to be the only abdominal organs which play a rôle in the disappearance of renin from the body.

4 Abdominal operation under chloralose anesthesia may be followed by a delay in the disappearance of injected renin. In one dog with the picture of shock, an increase in the concentration of renin in the blood was observed.

5 After the intravenous injection of amounts greater than 2 c.c. of renin, a fraction of it was found in the urine. The excretion of renin in the urine does not seem to be an important mechanism in the disappearance of renin from the body and does not account for the delay observed in recently nephrectomized dogs as compared with normal dogs.

6 No neutralizing or destructive property against renin was demonstrable in blood drawn from the jugular vein, carotid artery, hepatic veins, or renal vein.

7 In uremic dogs there is a slow disappearance of injected renin from the blood. The delay in the disappearance is attributable to an alteration of the destructive action of the tissues rather than to a lack of some substance in normal blood which destroys renin because the disappearance of injected renin from the blood is not faster in uremic dogs with approximately 87.5 per cent normal blood and is not modified in recently nephrectomized dogs with approximately 75 to 87.5 per cent uremic blood.

8 It is concluded that although the kidney seems to have some destructive action, destruction of renin by the tissues is the principal factor in its disappearance from the blood. The mechanism by which the kidney and the body tissues destroy renin has not been demonstrated.

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STUDIES ON THE ETIOLOGY AND SERUM TREATMENT OF ENCEPHALITIS DURING THE EPIDEMIC IN NORTH DAKOTA AND MINNESOTA (1941) *

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WE have had opportunity to study the etiology of encephalitis as it occurred during the summer and autumn of 1941 and to observe patients while they were under treatment with the encephalitis antistreptococcic serum

CLINICAL STUDIES

The patients with encephalitis observed in this epidemic presented striking similarities in symptomatology and appearance. Headache, nausea and vomiting with fever were the cardinal symptoms. Patients who had the severe forms of the disease were striking in appearance, not infrequently the patients were irrational, many were lethargic and had lost sphincteric control of the bladder and rectum. Rational patients complained bitterly of severe headache which had failed to respond to the usual medications. These patients at times complained also of vertigo, blurred vision and sore throat. In some cases the headache and nausea were unbearable, and the chief complaints were of weakness, backache and ataxia. The onset of the disease often was abrupt, heralded by chills or chilly sensations and headache. Great variations in the severity of symptoms were frequently evident.

From the onset the local physicians, as well as ourselves, were struck with an unusual odor often present at the bedside of the patient. Examination usually revealed acutely ill patients with flushed faces. Their eyelids often appeared swollen and the conjunctivae were injected. Even petechial hemorrhages were noted. Nystagmus was rare, and in no case was ocular paralysis noted. Various degrees of rigidity of the neck, and even opisthotonos among children, were present. The pharynx and soft palate usually were definitely injected. Usually no neurologic changes were demonstrable, aside from hypoaactive reflexes, vertigo and ataxia. Localized spasms and even generalized convulsions were observed in some cases. In two patients bulbar paralysis developed before death.

The urine was consistently normal except for occasional specimens in which traces of albumin were found. In only one case was there evidence of pyelonephritis.

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We are indebted to Dr E J Larson, Jamestown, North Dakota, Dr A C Baker, Fergus Falls, Minnesota, and their colleagues and to H J Larson, D. V. M., Fergus Falls, Minnesota, for their cooperation.

Blood counts showed an average of about 10,000 to 14,000 white blood cells, however, in classic cases a normal leukocyte count often was obtained. The leukocyte counts ranged from 5,000 to 28,000 cells.

The cellular response in the spinal fluid resembled closely that which occurs in epidemic poliomyelitis and that which characterized epidemic encephalitis during the St. Louis outbreak^{1,2}. In a few cases in which unmistakable symptoms were present the spinal fluid was free from cells. The highest count obtained was 695 cells, the average being 150 cells. Polymorphonuclear cells predominated at the onset, and lymphocytes predominated in the later stages of the disease.

Sections of the brains of patients who died revealed typical lesions of encephalitis (figure 1).

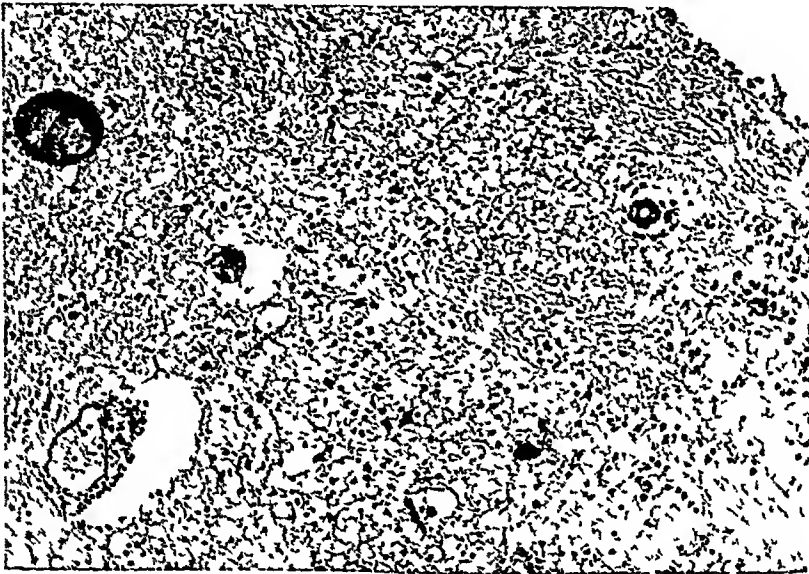


FIG 1 Perivascular and parenchymatous infiltration and degeneration in the pons of a patient who died (hematoxylin and eosin $\times 105$)

The manner of spread and the incidence of the disease were strikingly like those in epidemic poliomyelitis. No age group appeared to be immune. We saw patients of widely different ages, ranging from five weeks to 82 years. Males, regardless of age, were more often stricken than females, as in epidemic poliomyelitis, the total ratio of males to females being 3 to 1. No females less than five years of age were affected, whereas eight males two and a half years to five weeks of age contracted the disease. There was, of course, no difference in exposure to mosquitoes of female and male babies. Evidence of contact infection, as in encephalomyelitis in horses, was almost wholly lacking. Not once did we encounter more than one instance of the disease in a family group. Patients were observed who gave histories of contact with horses, cattle, sheep or dogs which had symptoms or had died of encephalitis. Mild types of illness, associated often with sore throat, with or

without fever, and severe headache, occurred commonly in one member or more of the family at about the time an undoubted instance of the disease occurred, as well as generally within the epidemic zone. We were impressed by the frequency with which instances of the disease occurred in remote regions, far from main routes of travel. In fact, most of the patients were brought to the hospitals from widely separated farms and gave no history of contact with the disease in human beings.

BACTERIOLOGIC AND SEROLOGIC STUDIES

On examination of smears of the sediment of centrifugated spinal fluid stained by Gram's stain or by means of a special staining method³ immediately after spinal puncture, the technicians and physicians at the Jamestown and Trinity Hospitals at Jamestown, North Dakota, found diplococci in 28 of 55 specimens in which search for organisms was made. We have corroborated and extended these observations and have succeeded in isolating streptococci from the spinal fluid (cultured immediately) of patients who had acute forms of the disease (figures 2*a*, *b*, *c* and *d*). Examination of speci-

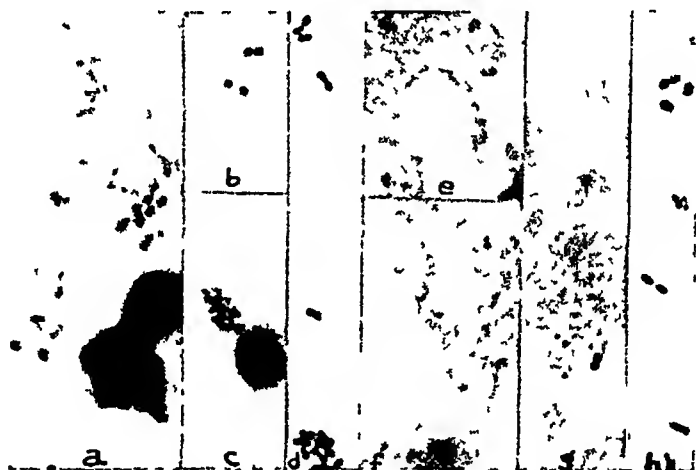


FIG 2 Diplococci and streptococci in and from the cerebrospinal fluid of four (*a*, *b*, *c* and *d*) patients during the acute stage of epidemic encephalitis, and in and from the brain of a patient who died (*e*, *f*, *g* and *h*), *a*, *b* and *c*, in the sediment of the cerebrospinal fluid, *d*, in pure culture in dextrose-brain broth, *e*, *f* and *g*, in degenerating ganglion cells and the interstitial tissue shown in figure 1, and *h*, in a dextrose brain-broth culture of the emulsion of the brain, *a*, stained by a special method³, *b*, *c*, *d* and *h*, stained by Gram's method, *e*, *f* and *g*, stained by a modification of Weigert's method⁵ ($\times 1000$)

mens of spinal fluid mailed to us, and reexamination after storage showed marked reduction in the cell count or complete autolysis of cells, and in no instance were organisms found or isolated.

It should be understood, of course, that the streptococci which have been isolated consistently in studies of poliomyelitis and encephalitis and referred to as such in this paper and in previous papers^{1,2} occur in spinal fluid and lesions chiefly as diplococci or ovoids (figures 2*a*, *b*, *c*, *e*, *f* and *g*), the former often resembling pneumococci, and in cultures as diplococci and diplococci coupled in chains (figures 2*d* and *h*).

By the use of media containing brain substance, and by other special methods,¹ streptococci which had a specific affinity for the brains of animals in the experimental laboratory and other specific properties were demonstrated or were isolated consistently from nasopharyngeal swabbings, from the stools, from the brain (one case, in which the outcome was fatal), from the spinal fluid of patients, and often from the throats of well "contacts" and well "noncontacts." On intracerebral inoculation of animals with highly diluted (1 to 10,000 to 1 to 100,000,000) cultures of the streptococcus obtained from each of the sources mentioned, the symptoms observed among patients—tremor, muscular spasm, nystagmus, ataxia, excitation, evidence of pain in the head and extremities, lethargy, circumcorneal congestion and subconjunctival hemorrhage, retrobulbar congestion and edema which often produced bulging eyes, cyanotic congestion of the mucous membrane of the trachea and hemorrhagic edema of the lungs sometimes associated with bronchopneumonia (expressive of the respiratory infection in patients)—all have been reproduced. The results in the aforementioned animals resembled closely those obtained in two monkeys, in rabbits, guinea-pigs and mice after inoculation of an emulsion, or filtrate of an emulsion, of the glycerolated brain obtained in one case in which the disease was fatal. This is as should be expected, because the streptococcus was isolated from and demonstrated microscopically in the lesions of this patient's brain, as in the brains of other patients dying of lethargic encephalitis^{2, 5} and in the brains of horses that died of equine encephalomyelitis.⁶ The glycerolated brain was sent to us by Dr. E. J. Larson of Jamestown, North Dakota. From the brains of animals that succumbed to the inoculation of cultures of the streptococcus, as well as from the brains of those receiving the emulsion or filtrates of corresponding brain tissue (virus), the streptococcus usually was isolated in pure cultures. Moderate to severe congestion and punctate hemorrhages of the brain, without clouding of the meninges, were found consistently in these animals. In the early stages of the experimentally produced disease, as in the disease among patients, the cells in the spinal fluid were chiefly polymorphonuclear, whereas, later, lymphocytes predominated. Diplococci were readily demonstrable in stained smears during the early stages of the experimental disease, but not in the late stages.

The intracutaneous injection of the water-insoluble (euglobulin) fraction of the serum of horses immunized with the streptococci isolated respectively from persons and horses ill with this disease, and with the western type of virus of equine encephalomyelitis, has been uniformly followed by an immediate erythematous-edematous reaction which did not occur, or which occurred to a far less degree, at the sites of control injections. This specific reactivity to the intracutaneous injection of the encephalitis euglobulin persisted for two to three weeks or longer among patients not treated with the serum, whereas among patients who received therapeutic intramuscular injections of the antistreptococcic serum this reactivity of the skin disappeared or became less marked within a half hour to four hours, to recur to a milder

degree if injections of antiserum were discontinued. In all patients tested it had disappeared completely after serum sickness. This was true of human and equine streptococcic euglobulins and the western type of "viral" euglobulin alike.

A specific precipitation reaction was consistently obtained between cleared extracts of nasopharyngeal swabbings and human and equine antistreptococcic sera and three commercial preparations of antiserum produced with the western strain of equine encephalomyelitis "virus." Cutaneous and precipitation tests with the antistreptococcic sera have been made previously, whereas those with the equine antiviral sera have not. By means of the precipitation reaction encephalitic streptococcic antigen was consistently demonstrated in the serum of patients as well as in the serum of horses and other animals ill with symptoms of encephalitis and in the spinal fluid of patients during the acute stage of the disease.

The streptococci isolated from the nasopharynx, stools, brain and spinal fluid of patients, and from the brain of horses and other animals having encephalitis, or which had died from it, were agglutinated specifically by the human and equine antistreptococcic sera, by the equine encephalomyelitis antiviral serum (western type), and by the serum of patients convalescing from encephalitis.

The "encephalitic" type of streptococcus was isolated from the blood and nares of horses, from the brains of sheep, a dog, a hog, chickens, a goose, and a pheasant which were ill or had died with symptoms of encephalitis in the epidemic zone. It was isolated from the brains of wild ducks which were ill and also from the brains and spinal fluid of fish dying in lakes, the water of which yielded the same streptococcus. Moreover, streptococci having "encephalitic" properties were isolated consistently from flies and mosquitoes, from milk, from water of wells in regions in which the disease had occurred, and from the air of rooms occupied by persons or stalls occupied by horses ill with this disease.

Chick-mash medium, dextrose-brain broth, distilled water, and small glass tubes and bottles coated with mineral oil, and tubes with screened ends filled with oiled spun glass or oiled glass beads were exposed to outdoor air in different cities and in the country at ground levels, and at levels as high as 21 stories of a building, at the front of an automobile that was being driven many hundreds of miles in wide areas of the epidemic zone, and at high levels, 1,000 feet or more, in an airplane that was flown by Dr. J. H. Pratt and one of us (Caldwell) over the same routes as those traversed with the automobile while samples at ground level in the epidemic zone had been obtained a few days previously. The "encephalitic" type of streptococcus was consistently isolated and "encephalitic" streptococcic and "viral" antigen were demonstrated by the precipitation reaction in most specimens obtained in stationary and mobile sampling at or near ground level, and the streptococcus was isolated in 60 of 94 cultures made from samples obtained during airplane flights of about 1,000 miles in the epidemic zone. Control samples

of air obtained at ground levels outside the epidemic zone rarely yielded streptococci, and yielded streptococcic antigen in only two of 14 samples

Moreover, cultures and extracts, in solution of sodium chloride, of dust obtained from filters used in air-conditioning units consistently have yielded the "encephalitic" streptococcus and the "encephalitic" streptococcic and "viral" antigen in large amounts. The details of these experiments and those on the relationship of the streptococci to the so-called virus will be published elsewhere.

TREATMENT WITH SERUM

The treatment of patients with serum was started during the peak of the epidemic of encephalitis at the two hospitals in Jamestown, North Dakota. Patients who had contracted the disease earlier in the epidemic at Jamestown, as well as those studied throughout the epidemic at Fergus Falls and other smaller outbreaks, who did not receive serum because of unavoidable circumstances, served as controls for members of the serum-treated group. There was no apparent difference in the matter of severity of illness, age, sex and other conditions between the serum-treated group and the nonserum-treated group. Many of the patients received one or another of the sulfonamide compounds, usually sulfapyridine or sulfathiazole. In accord with results of experimental studies,^{7,8,9} there was little clinical or objective evidence that these drugs exerted beneficial action, either when they were administered alone or when they were given in conjunction with the serum (table 1). Only patients for whom a diagnosis could be made definitely by

TABLE I
Results of Treatment with Encephalitis Antistreptococcus Serum

Groups	Cases	Average Duration of Fever Days	Deaths	
			Number	Per Cent
Patients not treated with serum who recovered	20	10.9		
Patients treated with serum who recovered	56	7.2		
Patients treated with serum soon after onset of symptoms—first or second day	15	6.3		
Patients treated with sulfonamide compounds only	5	10.4		
Patients treated with serum only	18	6.7		
Patients treated with sulfonamide compounds and serum	38	7.9		
Total patients not treated with serum	27		7	26
Total patients treated with serum	70		3	4.3

means of spinal puncture or the classic signs and symptoms of the disease received serum treatment, and there was no selection of patients.

The results of treatment with serum appeared to be strikingly favorable, especially when treatment was started early in the course of the disease. The effect was even more marked in relief of such symptoms as the distressing

headache (such relief often occurring in a few hours), as well as relief of nausea and vomiting, than the effect on the duration of fever (table 1) and the temperature curves would indicate (figures 3, 4, 5 and 6) Not infrequently headache completely subsided overnight, whereas the signs of the disease, such as rigid neck, still persisted

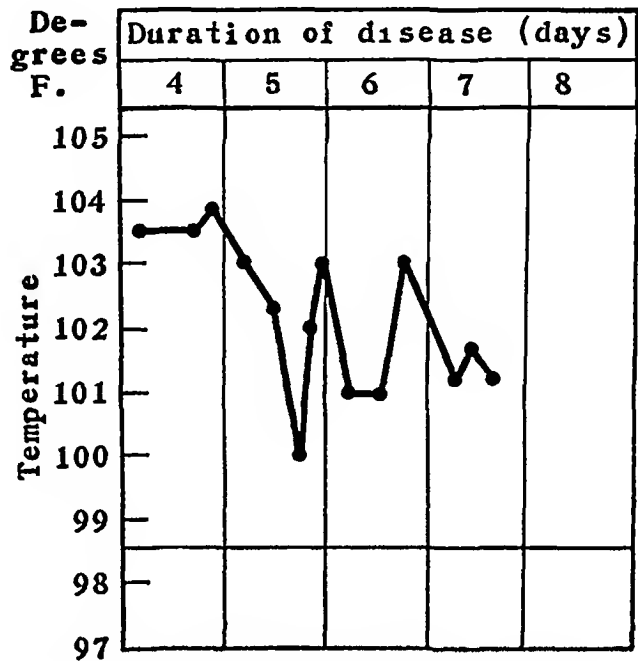


FIG 3 Temperature curve, patient in case 1

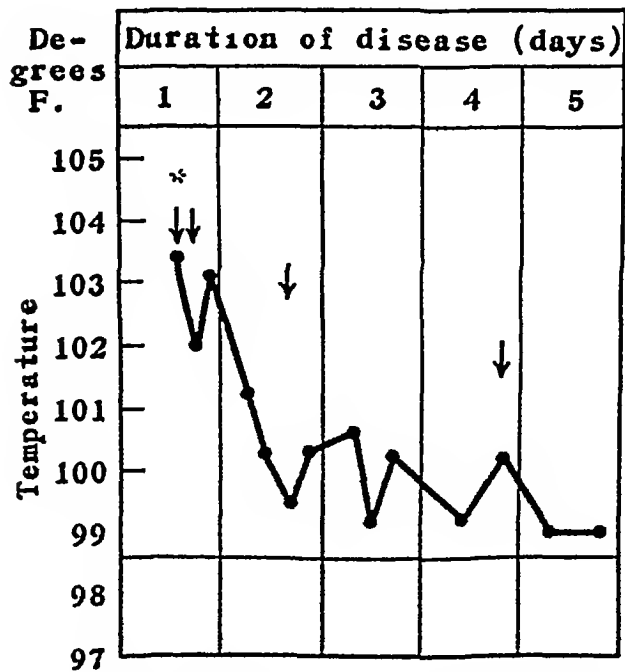


FIG 4 Temperature curve, patient in case 2

* The arrows indicate the time of injection of 17, 10, 10 and 5 c.c. of the antistreptococcus serum, respectively

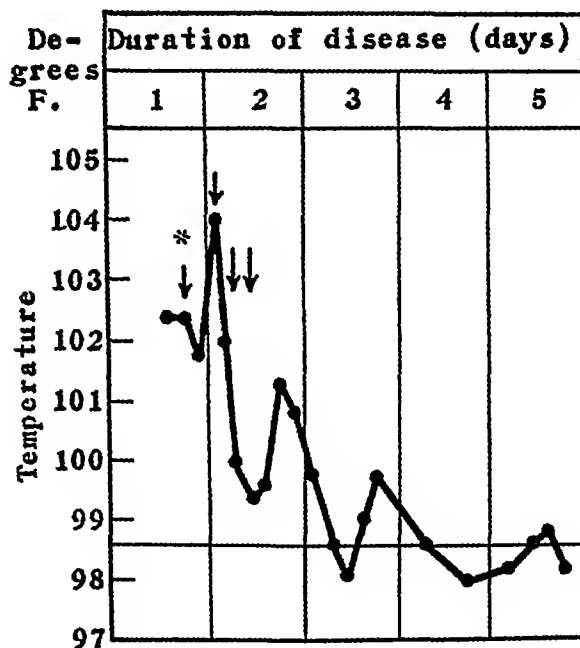


FIG 5 Temperature curve, patient in case 3

* The arrows indicate the time of injection of 10, 10, 5 and 15 c c of the antistreptococcus serum, respectively

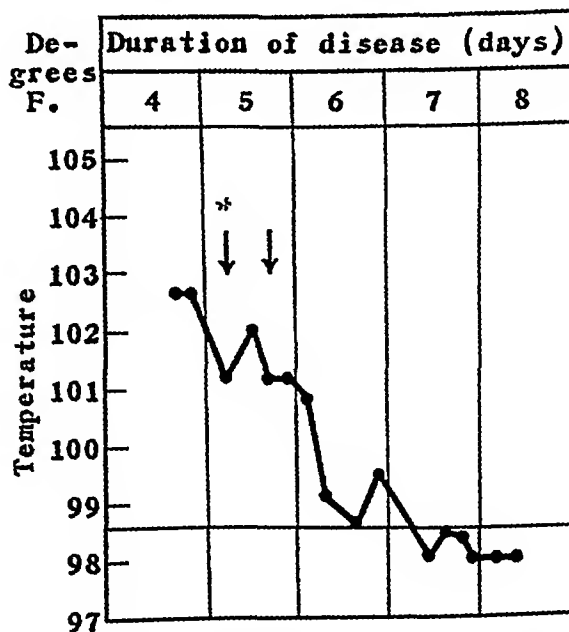


FIG 6 Temperature curve, patient in case 4

* The arrows indicate the time of injection of 10 and 10 c c of the antistreptococcus serum, respectively

The dosage of the serum was changed in the latter part of the epidemic, and the change resulted in what was felt to be a more favorable response. Patients treated earlier in the epidemic received 10 or 20 c c by intramuscular injection once or twice daily. Later, because of the frequency with which reactions to cutaneous tests returned to positive, the dosage was changed to 5 c c injected intramuscularly at four-hour intervals. A secondary increase in temperature was prevented in this manner. We noted not infrequently that when treatment with serum was discontinued, a secondary increase in temperature appeared, and for this reason we recommend that the treatment with serum be continued for at least one day after the temperature has returned to normal. No untoward reactions followed the use of the serum, except for an occasional temporary increase in temperature as an immediate reaction. Hives developed among most of the patients as a late reaction to the horse serum.

The antistreptococcic serum was produced in horses by the injection of streptococci that had been isolated during studies of encephalitis, the antigenic specificity of the streptococci was maintained throughout the long period of immunization.¹⁰

The following cases have been chosen to typify the extremes in age groups attacked, as well as to emphasize the value of serum therapy when it is administered early, and also to present the variations in symptomatology and laboratory observations among patients ill with encephalitis.

CASE REPORTS

Case 1 (figure 3) A 48-year-old farmer was admitted to the Jamestown Hospital complaining chiefly of severe headache, more severe than and unlike any he had experienced in the past. Associated with the headache were persistent nausea and occasional vomiting. These symptoms had been present for four days.

Examination revealed an acutely ill man whose face was flushed, whose conjunctivae were injected, whose throat was diffusely red and whose neck was rigid. Spinal puncture on admission of the patient and examination of the cerebrospinal fluid revealed 37 cells with 15 per cent polymorphonuclear leukocytes per cubic millimeter. Two days later spinal puncture and examination of the spinal fluid revealed 205 cells per cubic millimeter.

The patient's course in the hospital declined progressively. He became irrational and comatose and died on the seventh day of his illness. No serum was given.

Necropsy was carried out by Dr. E. J. Larson, and the brain was sent to the Department of Pathology of the University of North Dakota, where the following report was made: "The entire brain shows marked congestion of the meningeal vessels, especially in the parietal region and over the cerebellum. Some arachnoid roughening along the longitudinal sulcus. Microscopic marked congestion of the vessels, perivascular infiltration of lymphocytes, plasma cells and few polymorphonuclear cells in the brain stem and cerebrum."

Case 2 (figure 4) A farmer 61 years of age was admitted to the Jamestown Hospital on Dr. G. H. Holt's service. This patient had become ill while he was working on a wheat binder. He came to Jamestown and was there found unconscious on the street by friends who brought him to the hospital. After regaining consciousness he complained chiefly of an inability to walk straight or, as he remarked,

"I can't track right" The patient also complained of severe headache and nausea which also had begun on the day of his admission

Examination revealed a very ataxic, well-developed and well-nourished man with a temperature of 103.4° F (39.6° C) His face was flushed and the mucous membrane of the conjunctivae and soft palate was severely injected Results of neurologic examination, except for hypoactive knee jerks and a rigid neck, were negative

Examination of the cerebrospinal fluid revealed 160 cells per cubic millimeter and diplococci in the stained sediment

This patient received about 30 c c of serum in two injections and on the next morning was able to walk so much better and his headache was so greatly relieved that he thought himself well enough to return to his work He was kept in the hospital, however, until he had completely recovered, after he had received a total of 42 c c of serum

This case well exemplifies the value of the administration of the serum early in the treatment of encephalitis Reactions to cutaneous tests were positive for encephalitis on the day of the patient's admission and were negative the next morning after the patient had received serum

Case 3 (figure 5) A 74 year old man was admitted to the Trinity Hospital on Dr F O Woodward's service He complained of severe headache and fever with chills of six hours' duration

Examination revealed the classic signs of encephalitis temperature 102.4° F (39.1° C), moderately stiff neck, and congestion of the face and mucous membranes of the eyes and soft palate Five lymphocytes per cubic millimeter were found in the cerebrospinal fluid and the blood leukocyte count was 8,000 cells per cubic millimeter

The headache and other symptoms disappeared overnight, after four injections of the serum, and the temperature receded rapidly to normal

This case also demonstrates the value of early treatment with the serum of patients ill with encephalitis

Case 4 (figure 6) An eight year old child was brought to the Trinity Hospital, complaining of headache with nausea and vomiting of four days' duration Dr E J Larson examined the child and made the diagnosis of encephalitis The reaction to the cutaneous test was positive Sixty-five cells per cubic millimeter were found in the cerebrospinal fluid Stained smears of the cerebrospinal fluid revealed diplococci The leukocyte count was 11,500 cells per cubic millimeter The symptoms rapidly subsided and the temperature receded to normal within 24 hours after two intramuscular injections of the serum

Case 5 A woman 23 years of age was admitted to the Trinity Hospital on Dr Holt's service, complaining of generalized headache unrelieved by acetylsalicylic acid (aspirin) There was no complaint of nausea or vomiting

Examination revealed a moderately ill woman, whose temperature was 103.4° F (39.6° C) Results of the general examination were normal, except for definite injection of the nasopharynx and stiff neck, and those of neurologic examination were normal The reaction to the cutaneous test was positive The leukocyte count was 11,500 cells per cubic millimeter Seventy-two polymorphonuclear cells were found in the cerebrospinal fluid Examination of the stained smear failed to demonstrate diplococci

Serum therapy was started at once and on the third day the patient was able to leave the hospital, after having received a total of 40 c c of the serum

Case 6 A farmer 63 years of age became suddenly ill with rightsided hemiplegia one week before his admission to the hospital on July 24, 1941. Apparently he had been perfectly well before the onset of this illness.

Results of the examination, aside from hemiplegia and rigid neck, were normal. The temperature was 102° F (38.8° C). Encephalitis was suspected and spinal puncture revealed 400 cells per cubic millimeter of spinal fluid, of which 15 per cent were polymorphonuclear leukocytes. A stained smear of the sediment of the spinal fluid revealed a few cocci. The urine was normal and the leukocyte count was 17,200.

The encephalitis antistreptococcic serum was not available at this time and the patient died the next morning.

Necropsy was performed by Dr. E. J. Larson and the pathologic report from the University of North Dakota follows:

"There is marked congestion of the meningeal vessels, with petechial hemorrhages in the medulla and base.

"Microscopic: Brain stem, midbrain and cerebrum. Congestion of the vessels, perivascular lymphocytes and polynuclear infiltration, perivascular hemorrhages and petechial hemorrhages.

"Diagnosis—encephalitis."

This case is of interest in that organisms were found in the spinal fluid of this patient proved to have had encephalitis. The patient was not seen by either of us.

In addition to the striking clinical improvement which followed injection of the serum, there was a shortened average duration of fever from 10.9 days to 7.2 days (table 1), a prompt recession in temperature, especially when the serum was administered in the early stages of the disease (figures 3 to 6), and a sixfold lowering of the mortality rate among members of the serum-treated group (4.3 per cent) over the rate among members of the control group (26 per cent, as seen in table 1). These results are favorably comparable to the specific serum treatment of pneumonia and to results reported previously in the serum treatment of encephalitis^{11, 12}.

In order to guard, in so far as possible, against recurrence and development of the so-called sequelae among persons recovering from this disease, sequelae which our studies have shown to be associated with the effects of neurotropic types of streptococci, it is suggested that all patients receive a series of injections of a detoxified vaccine prepared from strains of the streptococci freshly isolated during this epidemic. This vaccine and the anti-serum are available for study.*

CONCLUSIONS

On the basis of our studies we are forced to the conclusion that encephalitis is caused primarily by a specific type of streptococcic infection, that the virus is related synergistically or phasally to the streptococcus isolated, and that the serum of horses immunized with this streptococcus is curative.

* Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

The presence of this particular type of streptococcus among persons and animals ill with this disease, and in well "contacts" and "noncontacts," and its wide prevalence in nature, including the outdoor air in the epidemic zone, are believed to be of great epidemiologic importance, and indicate that the disease may be air-borne

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PSYCHOLOGIC ASPECTS OF HEART DISEASE *

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A review of the literature on heart disease in which psychologic factors are discussed constitutes an interesting experiment for the internist as well as for the psychiatrist, for not only is the internist likely to be bewildered by the psychiatric terminology and interpretations, but the psychiatrist feels equally confused on reading the papers in the field of internal medicine

Articles by Paul White,^{1,2} Reid,³ Hirschboeck,⁴ Edwards and White,⁵ and Friedlander and Levine⁶ stress the sharp differentiation between organic heart disease and so-called "cardiac neurosis" This is also the chief point made by Boas,⁷ Willius,⁸ and Jukes⁹ Emphasis is placed by several writers on the importance of diagnosing the neurosis by exclusion of organic disease, whereas in no instance with the above is a psychologic disease assigned a major rôle in the etiology of coronary occlusion or the syndrome of angina pectoris

Turning to the writings of psychiatrists and neurophysiologists there should be little surprise to find that an attempt has been made to show a true relationship between psychic phenomena and certain types of heart symptoms, and that the nature of the rôle of psychic phenomena in the causation of organic heart disease is the subject of considerable psychiatric research at the present time William Menninger^{10,11} has reviewed the literature and offered a method of classification which we shall not give here He emphasized the importance of the psychiatric point of view in the study of organic diseases of the heart Menninger suggested the following as possible steps in the production of some forms of heart disease first, an emotional disorder causing functional heart disorder, the disturbance continuing for a protracted period of time, second, the continued functional disorder giving rise to structural changes in the form of organic heart disease Yaskin¹² strongly maintained the inadvisability of using psychic and somatic complaints as criteria for diagnosis He emphasized the fact that the sympathetic nervous system is subject to emotional factors which affect the heart both directly and also indirectly through alteration of the epinephrine content of the blood, which in turn acts on the heart Sonia Wiess,¹³ writing in 1932, discussed the effect of the so-called "emotional storms" on blood pressure and the peripheral vascular bed Wolfe,¹⁴ in 1934, wrote of the intense repression with anxiety found in patients with "cardiac neurosis" Katzenelbogen,¹⁵ in writing of somatic disorders of functional origin, pointed to the frequency of autopsies of patients who had coronary sclerosis without symptoms and also of those who had typical angina pectoris without coronary disease or disease of the sympathetic nervous system Although he did not so state he strongly

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implied that psychologic factors often play a major and deciding rôle in the production of angina pectoris. Conner¹⁶ mentioned the important rôle of profound grief and prolonged anxiety as a cause of certain cardiac disorders. Kerr, Ghebe and Dalton¹⁷ described the physical phenomena found in anxiety states. These authors spoke of a "hyperventilation syndrome." The chain of circumstances in this syndrome, according to them, was as follows: the individual is faced with a problem to meet, he may face it squarely or attempt to ignore it. If an attempt is made to ignore it, it is the suppressed emotion associated with the conflict that directly stimulates the sympathetic nervous system. This stimulation occurs through the centers of the sympathetic nervous system in the cerebral cortex and the basal nuclei, reaching the heart in the rich plexus of sympathetic fibers arising both from the cervical ganglia and the upper five thoracic nerves. Stimulation of the adrenal glands also occurs, which in turn probably stimulates the heart. There is increase in respiratory rate and in ventilation, with carbon dioxide expelled from the blood stream and the tissues to the alveolar spaces. There is retention of chlorides and phosphates in the blood, with alkalosis, and a resultant irritability of muscle tissue. Others have attributed the symptoms to a constriction of the coronary vessels supplying the heart with blood, due to overstimulation of the sympathetic innervation of the heart, with a resultant asphyxia and myocardial damage. Most authors emphasize the importance of careful psychiatric study of the patient, with relief from conflict as the primary immediate therapeutic goal. Houston¹⁸ pointed out that the term "cardiac neurosis" indicated a profound learned reaction of the heart and its blood supply, which he termed a "spasmogenic aptitude." He suggested that the response of some individuals to early fears and "unpleasant efforts" produced a conditioned response to similar stimuli.

H. B. Day,¹⁹ writing on the "emotional causes of somatic disease," stated that he believed that the physiological effects of emotion may, under certain circumstances, become habitual and result in pathological structural change. Deschanps²⁰ and Brosse²¹ mentioned changes in the electrocardiogram which ordinarily would be interpreted as evidence of organic heart disease, produced, however, by intense concentration of attention as practiced by the Yogis in India. Delius²² urged the use of the electrocardiogram to detect the transition between functional and organic heart disease. He stated that there was a relationship between subjective pain and changes of rhythm. He stated that many cases during the war diagnosed as "neurotic" might have been found to be organic with electrocardiographic examination. He suggested use of the term "functional cardiac disorder" rather than neurosis in early cases, thereby recognizing the possibility of later structural change.

Dunbar²³ reported three cases with results of therapy at the psychologic level. She pointed out the growing tendency and need to give up our attempt to differentiate sharply functional and organic heart disease. This author also stressed that it is now possible to learn enough about a patient

so that psychic components in illness can be shown in casual sequences to allow diagnoses to be made at the psychologic level, rather than by exclusion of organic disease. Dr Dunbar reported three cases all helped through psychotherapy, by allowing the psychologic processes to come into conscious relationship with the symptoms. Family history of heart disease as a predisposing factor also seemed important and was present in the cases quoted. She strongly hinted that psychic and emotional factors played an important etiologic rôle and often hastened the development of invalidism and death.

Two cases are here reported, both having been studied from the psychiatric standpoint to a limited degree. The cases are reported because of the rather close relationship between the symptomatology and the psychologic background. In both cases there is history of long-standing so-called psychologic maladjustment, with symptoms which seem closely related and blend into a final "organic picture." Physical examinations and electrocardiographic findings point in both cases to the existence of organic change in the heart. If a long history of psychologic maladjustment, with the production of "tension," is capable of producing first a change in the function of the coronary vessels and later a change in the structure of the vessels, it is possible that one of the types of psychologic processes involved is illustrated in these cases. They are further reported because of their rather remarkable response to treatment at the psychologic level so far as relief of symptoms is concerned.

CASE REPORTS

Case 1 E S, aged 45, married, was referred to us March 17, 1937. His chief complaint was "heart trouble and crying spells." Family history revealed that the father died at 62 of "acute indigestion and heart failure." The patient was well until June 8, 1936, when he was seized with severe "pain over the heart" with a smothering sensation, a sense of pressure in the chest, and pain down the left arm. These symptoms were associated with a feeling of impending death and marked fear. The attack passed away in a few hours with morphine and rest. Two days later a second and more severe attack of a similar nature occurred and a diagnosis of coronary thrombosis was made by the attending physician. The patient remained in bed for a period of about eight weeks, during which time an electrocardiogram was done (figure 1). In this period of bed rest there were attacks of crying, depression, irritability and restlessness, with pain over the heart. The crying seemed to be without motivation, and suicidal thoughts came to him. There then followed a period at home during which he was mildly active physically. He was irritable toward his wife, was depressed, and suffered with pain over the heart and crying spells. In February 1937, he visited his brother in California, remaining there one month. For the first 10 days of the visit he was moderately free of symptoms and experienced a lessening of tension and a feeling of hopefulness. The pain returned during the second week of his stay, and he consulted a cardiologist who advised him to consult a psychiatrist on his return home. He was referred for examination and treatment March 17, 1937.

At the first interview the patient seemed cheerful on entering the office, but as soon as the door was closed he broke into convulsive sobbing which lasted for nearly an hour. He was occasionally able to inter-purse his crying with statements of his hopeless financial situation and profound depression. He was seen regularly thereafter.

over a period of two or three months, there was steady improvement of symptoms with complete cessation of them by June 1937. Most of the material discussed in the early interviews had to do with his progressively developing financial failure during the preceding two or three years. This had meant evading more and more those to whom he was indebted so that in the few months before the acute onset of his symptoms he had experienced intense remorse on looking over debts, especially those debts to personal friends. He had been avoiding his creditors on the street and was urged systematically to interview them and explain his financial status. For the most part however, he was urged to talk freely and as he pleased in the interviews. It is interesting that he reported relief within a week from the acute pain, smothering sensation, crying and depression, and had returned to work with plans for the future. Within this period, furthermore, he could use his visits more calmly to discuss the earlier parts of his life. How much his financial problems entered into his illness as a precipitating factor is illustrated by the fact that he had developed a dread of looking over his debts because of the agitation that act produced. The acute onset, furthermore, came while he was so engaged.

Psychiatric study over the subsequent two or three months revealed a long history of marked inferiority reactions during childhood and adolescence in the form of shyness, evasion of athletic competition, sensitiveness, masturbation with its attendant feelings of guilt, and the development of a proud haughty manner. He recalled witnessing arguments between his father and mother as early as the age of four, at which time pain over the heart with a sense of smothering occurred. He recalled at the age of nine phantasies of killing his father after such arguments. He reported two dreams of his mother being abandoned and being in need of him. He admitted that his wife was not the one with whom he was originally in love and recognized a greater need for his mother than for his wife. There was a period of self-inflicted isolation through adolescence to keep him away from "tough gangs" in his neighborhood, his fear of them being associated with "pain over the heart." The childhood masturbation continued into early adult life until his marriage. He reported intense feeling of guilt, with depression, lasting a day or two on several occasions following masturbation, this feeling of depression was accompanied by pain over the heart and down the left arm and a smothering sensation in the chest. The memories of the above combination of symptoms were clear to the patient, and care was exercised by the examiner not to suggest their presence.

He returned to work during the first week of treatment and after three weeks was working steadily full time. He has since remained continuously at work. Only with the nearly fatal illness of his older son did he experience pain in the region of the heart. Financially he was unable to have more than limited treatment and certainly not long psychiatric study. A total of 15 one hour visits was made, most of them within the first two months. In that time sufficient material was brought into relationship with consciousness to allow him to make a fairly good adjustment. He is cheerful, free of pain, and working steadily. Electrocardiographic studies are shown (see figures 1, 2 and 3), all of them with evidence of myocardial damage and interpreted as probably indicating a previous cardiac infarction. Clinical examinations supported these findings.

Although psychiatric study is incomplete and does not reveal the entire structure of the neurosis, sufficient information was obtained to indicate a psychologic process centered in the Oedipus situation with considerable persistent need for the mother and hostility toward the father. Marked inferiority reactions have continued from childhood to the present time with repression of attendant feelings of guilt. Cardiac pain, suffocation, fear and depression are traceable to the age of four. Attempts at compensation have produced a proud, haughty "extravert" type of behavior maintained for long periods of time, breaking down under stresses such as economic failure,

critical illness in the family, etc. There is laboratory and clinical evidence of organic heart involvement with relief obtained at the psychologic level.

Case 2 C R M, 45, married, was first seen June 27, 1939. At the time of the first examination his complaints were that he was depressed, had little interest in work and had feelings of fear, insecurity and of being different from other people. He also complained of pain and a smothering sensation in the chest. The pain passed into the left arm. He stated that the above group of symptoms always occurred when his

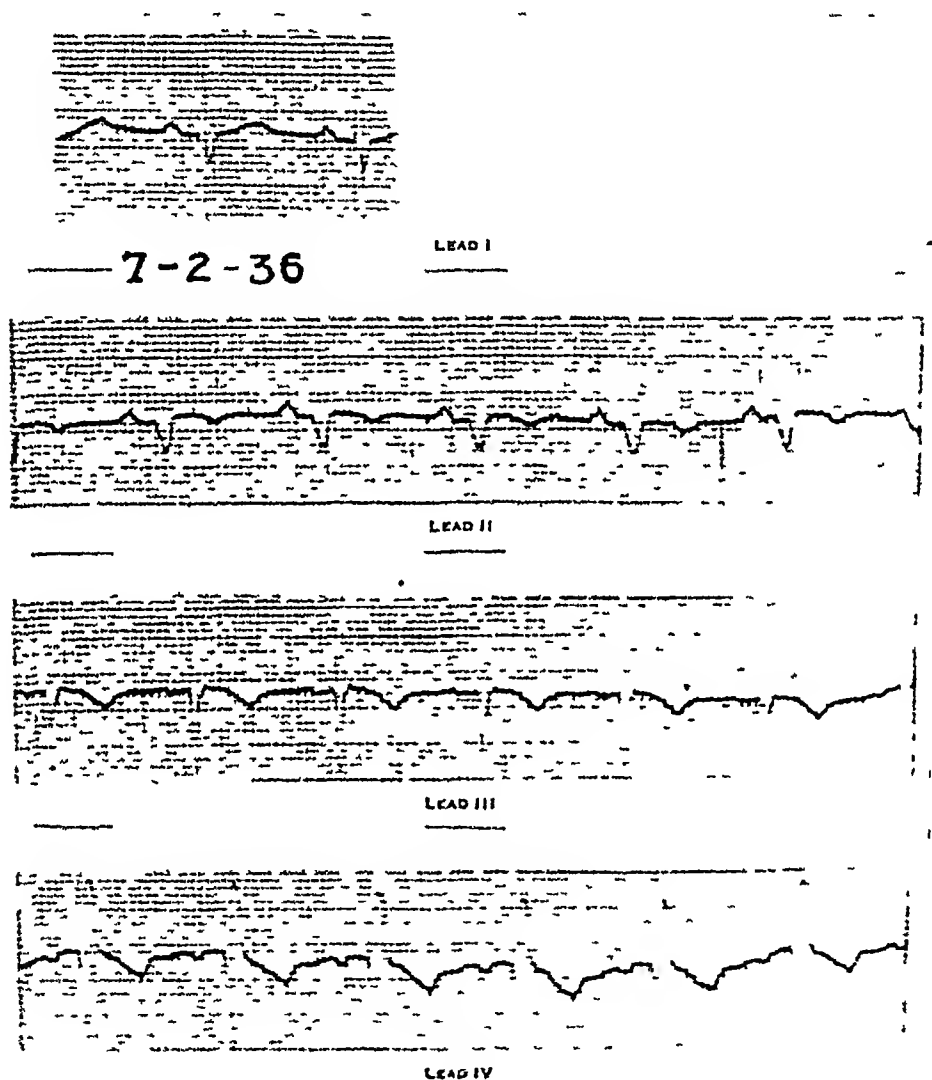


FIG 1 *Case 1* EKG, 7-2-36. Rhythm regular. Rate 60. T-waves sharply inverted, Leads II and III. Upright Lead I. Inverted Lead III. QRS. Left axis deviation, slight aberration. Conclusions: T-wave changes suggestive of previous posterior cardiac infarction.

wife was visiting out of town, leaving him at home alone. She was then out of town. At this interview, the patient told the examiner that he would not need care over an extended period of time because his wife would soon return from her visit and he expected his symptoms to disappear at that time. He volunteered the information that these same symptoms came whenever he was left at home for more than a day, but that he had been ashamed to ask a doctor about his fear and depression because he felt that he must be a "coward" to be afraid. Until this time, therefore, he had complained to his doctor only about the smothering sensation and the pain in the arm and chest.

He was seen twice within a few days and related the following history. He was born in Iowa. His father and mother had quarrelled violently from the period of his earliest memories. They separated when he was 15, at which time he was left to shift for himself. He recalled being greatly upset during these disputes and experiencing feelings of rage, fear, depression and a smothering sensation in the chest. He described this as a "tightening" that would last for a day or two after the quarrel had subsided. Fear of being alone was present as early as the age of 10. He associated

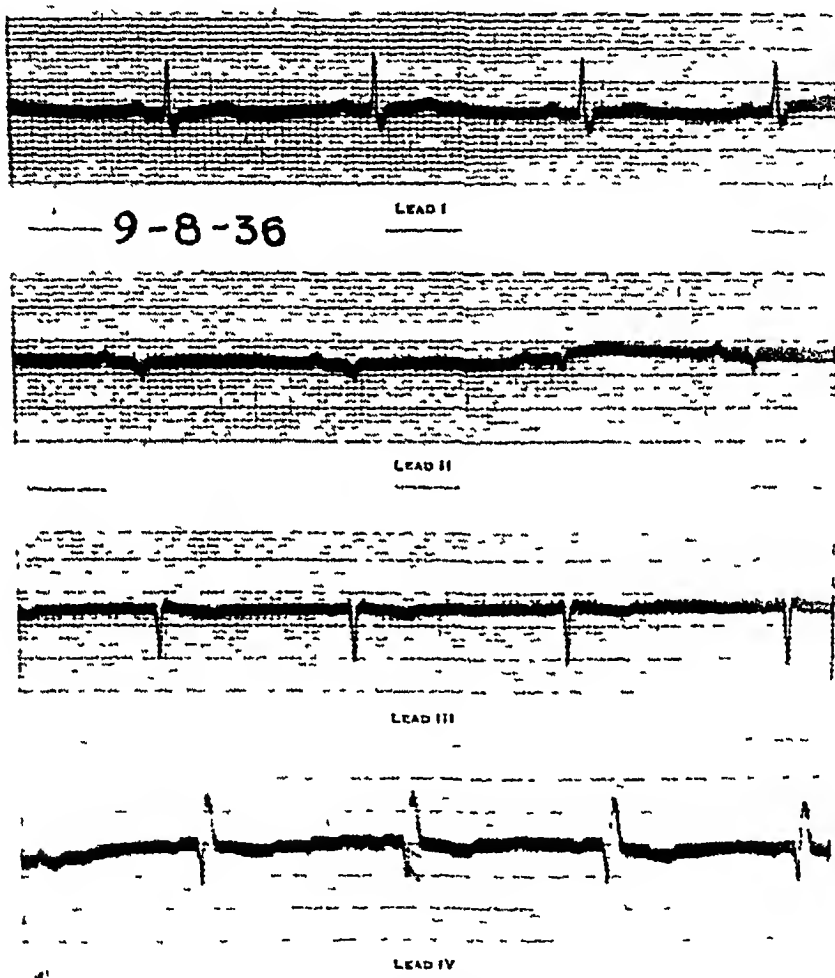


FIG 2 Case 1 EKG, 9-8-36 Since tracing 7-2-36 III is less inverted T_2 is now flat T_1 is now flattened. Conclusions: Changes suggest healing posterior cardiac infarction.

the rage and anger with his feeling toward his father during the arguments. He was left alone when 15, and there then followed years of hard work, lonely wandering and poverty in a battle for economic security that had been uphill until recently. From time to time until his marriage he experienced short periods of a day or two of depression, fear of something impending and smothering in the chest. His marriage brought him his first feeling of being wanted by someone. He could recall no similar feeling while living with his parents. Since his marriage he had been free of symptoms, except when his wife was visiting out of town. During her absence depression,

fear, loneliness and a tightening, smothering feeling in the chest were present. Beginning three years previously the above symptoms included pain over the heart. This pain varied from a dull ache to a severe piercing pain which passed into the left arm. He consulted a physician at the onset of the pain and an electrocardiogram was done (figure 4). A diagnosis was made then of coronary artery occlusion. He reported being free of pain and of his other symptoms, except during the occasional absences of his wife.

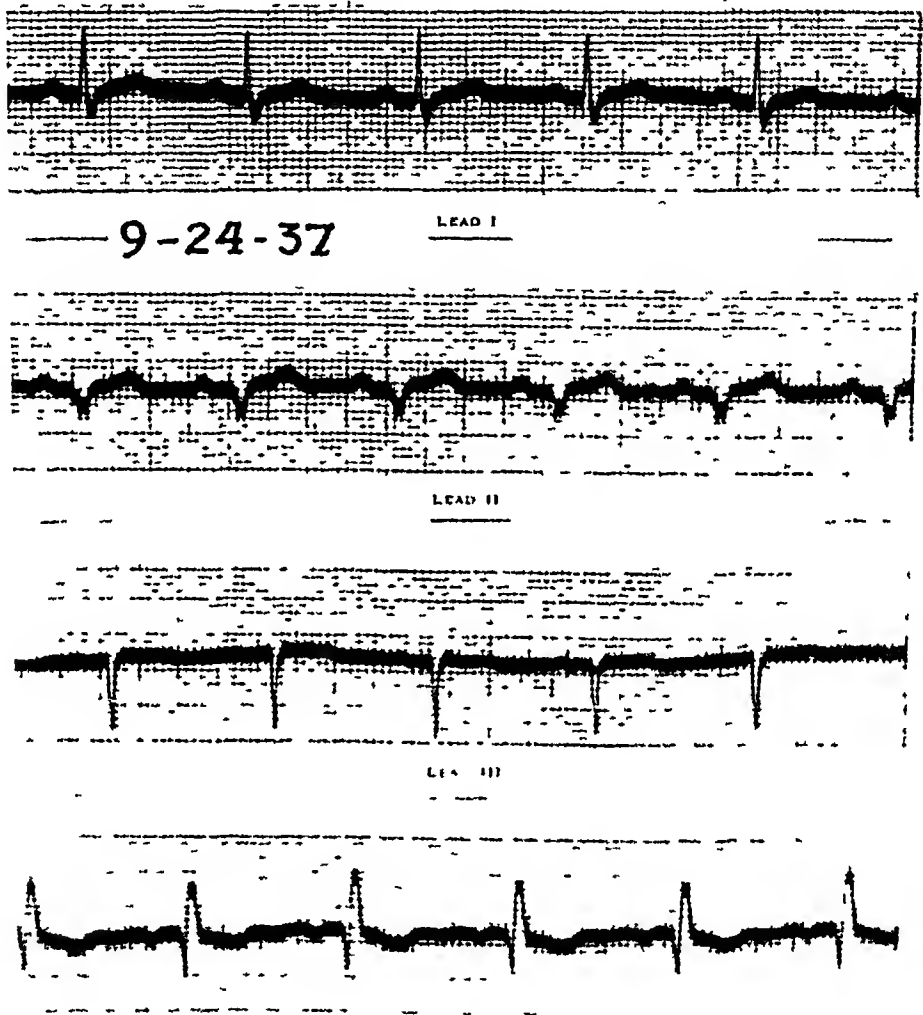


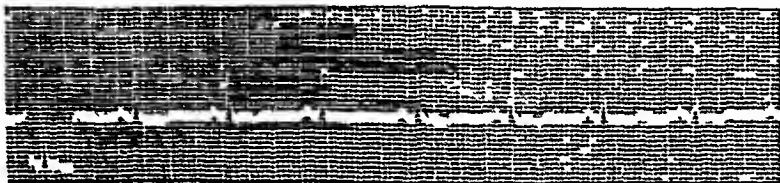
FIG 3 Case 1 LKG, 9-24-37 Rate 60 Rhythm regular T₁ now upright I₂ diphasic QRS Slight aberration Conclusions Changes suggest healing or healed posterior cardiac infarction

Therapy consisted only in assuring him that his fear and anxiety probably were related to earlier fears of being abandoned and that he showed no evidence of being a coward. The patient reported by telephone on August 25, 1939, that he had not returned for treatment because he had felt well since his last visit and inasmuch as his wife had returned from her trip a few days later he had remained well.

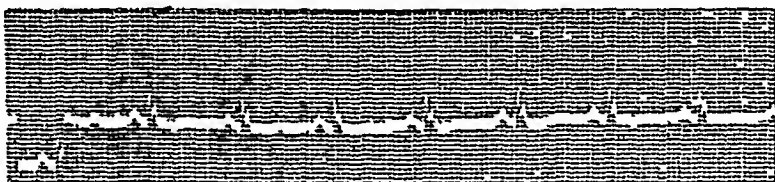
Although more complete psychiatric study was not possible, the patient was convinced of a close relationship between his childhood experiences and his present condition. This much seems evident: that deep resentment existed toward his father that

his childhood afforded him little love and security, and that at an early age he was forced into adult reality situations without sufficient preparation. In his own opinion his wife fulfills the obligations both of wife and mother to him. It seems reasonable, therefore, to assume that his symptoms represent his childhood and lifelong reaction to abandonment.

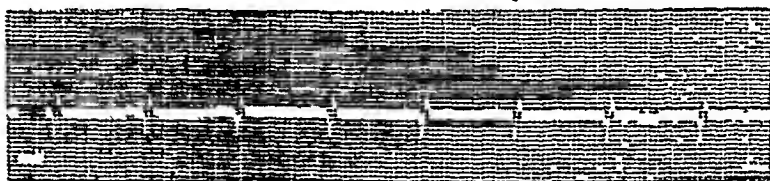
Lead I



Lead II



Lead III



Lead IV

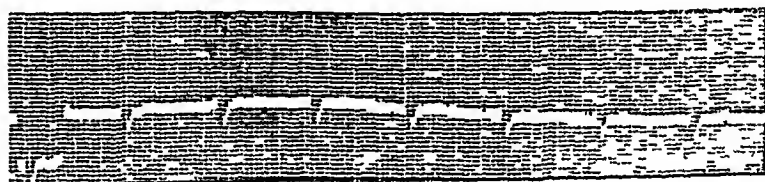


FIG 4 Case 2 EKG, 2-25-39 Sinus rhythm 75 QRS slurred in all four leads QRS duration .08 second T_1 is diphasic T_2 and T_3 are inverted Q_2 is of 4 mm amplitude. Conclusions These findings indicate myocardial damage, probably a result of coronary vascular disease, and suggest the possibility of posterior cardiac infarction.

DISCUSSION

In both cases there is a history of long-standing symptom complexes which follow a pattern rather accurately from early life to the present. Somatic symptoms of pain in the chest and down the left arm, together with

a smothering feeling in the chest, were present in Case 1 from the age of four. In Case 2 pain over the heart did not occur until the age of 42, however, smothering and a "tight" feeling in the chest, fear, loneliness and depression came during and following quarrels between the parents, at which times he also felt rage toward the father. The patient gave the age of eight as the approximate time when the symptoms first appeared. The threatened dissolution of the home seemed sufficient to precipitate the symptom complex. When pain over the heart and in the left arm joined the syndrome many years later, being alone, even though there was no threat of being abandoned, brought on the symptoms. The probable structure of the neurosis in each patient was based on the Oedipus situation with repressed rage against the father and longing and need for the mother. The quarreling of the parents seemed in each case to be a threat of abandonment, actually occurring in Case 2 and nearly so in Case 1. Heart pain, smothering sensations, fear and crying were recalled by the first patient, associated with the quarreling between the parents and carried into fantasies of abandonment by them. Thoughts of killing the father were present in Case 1, and in Case 2 there was intense anger toward the father. In Case 2 attacks were always precipitated by absence of the wife from home for more than a day.

Electrocardiographic examination in each case showed coronary disease. No definite conclusions can be drawn as to the interrelationship between the neuroses present and the cardiac disease. Both neurosis and cardiac infarction can be diagnosed to the satisfaction of both internist and psychiatrist in each case. Treatment at the purely somatic level failed to give relief in Case 1. Rest in bed aggravated the symptoms, and relief occurred only by bringing some of the conflict into relationship with consciousness. This type of therapy produced relief from both "somatic" and "psychologic" symptoms.

It is suggested that psychologic conflict of the above discussed type may create a flow of nervous energy to the vasoconstrictor mechanism of the coronary vascular bed over a long period of time and greater in volume than is found in individuals without such conflict. That secondary changes of an organic nature may take place in these vessels must be considered. Such a process is, however, difficult to prove.

SUMMARY

The case histories of two patients, each with a neurosis dating from childhood and associated later with coronary disease and cardiac infarction, are presented. The structure of the neurosis in each case centered about the Oedipus situation. Treatment at the psychologic level gave relief. Coronary disease is prominent among those whose psychosomatic relationships require further study. The above cases are offered as examples of one type of neurotic conflict which may be involved. It is felt that terminology should be freed of terms sharply delimiting the organic from the psychologic.

Study of "cardiac" patients at the psychologic level should prove fruitful, both for greater knowledge of psychosomatic relationships and for the more intelligent treatment of the patient

The author wishes to thank Drs Robert King and Austin Friend for interpretations of electrocardiograms and various suggestions as to terminology

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SPONTANEOUS HEMOPNEUMOTHORAX: REPORT OF THREE CASES AND REVIEW OF LITERATURE *

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INTRODUCTION

SPONTANEOUS idiopathic hemopneumothorax is an unusual clinical condition which develops when bleeding occurs into the pleural cavity during the course of a spontaneous pneumothorax

Three patients presenting this condition have been observed at Cleveland City Hospital during the last 10 years. The first two were observed on the medical wards within the last two years. The third was discovered as the result of a survey of cases of pneumothorax and of hemothorax observed at City Hospital during the years 1930-1940, excluding those cases in which active tuberculosis was known to be present

CASE REPORTS

Case 1 The first patient was a 26 year old machinist who had no history of previous serious illness. One week prior to admission to the hospital he was seized, upon arising from bed, with a sharp stabbing pain in the left chest which radiated to the left shoulder and then gradually spread to the right chest. He attempted to work but was forced to return home after two hours. The following morning while walking to the bathroom the patient fainted. On recovering consciousness he had a profuse sweat, and his family noticed that he seemed unusually pale. The pain in the chest subsided within two days, but he developed progressive weakness, dyspnea on exertion, and low grade fever. He also had a cough occasionally productive of small amounts of yellow sputum. Slight blood streaking had occurred on one occasion.

On admission the patient did not appear acutely ill, but his temperature was 38.2° C, he was dyspneic and appeared pale. Significant physical findings were confined to the chest. A respiratory lag and abnormal fullness of the interspaces were noted on the left. There were dullness, diminished tactile fremitus, and absent breath sounds below the level of the fifth interspace anteriorly and the third interspace posteriorly. Above this area the percussion note was tympanic, and a few moist râles were heard at the left apex. The heart was displaced to the right. Diagnostic aspiration revealed the presence of gross blood in the left pleural cavity. The red count on admission was 3,020,000, hemoglobin 55 per cent, and white count 13,500. Bleeding and clotting times and the capillary resistance test gave results within normal limits.

A diagnosis of left hemopneumothorax was made.

A roentgenogram of the chest taken on the day of admission showed a dense shadow occupying the lower half of the left lung field, with a fluid level overlying the fourth rib anteriorly. Above this level a pneumothorax was present. Four days following admission fluoroscopy revealed that the fluid had risen to the level of the clavicle. The patient at this time was moderately dyspneic, but the mediastinal displacement was not sufficient to cause circulatory embarrassment. Therapeutic aspiration yielded 1100 cc of fluid with a red cell count of 2,800,000. Four hundred cubic

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centimeters of air were introduced. Following this aspiration, the fluid was still at the level of the eighth rib posteriorly. The fluid was negative for pyogenic organisms, tubercle bacilli, and tumor cells. Sputum examination was likewise negative for tubercle bacilli.

A second aspiration done two days after the first yielded 1800 c.c. of fluid with a red cell count of 540,000. Two hundred cubic centimeters of air were injected. The fluid withdrawn failed to coagulate after two hours. A second roentgenogram taken at this time showed only a small amount of fluid at the left base. There was still a 50 per cent collapse of the left lung, and no evidence of parenchymal infiltration was present.

At a third therapeutic aspiration seven days after the first, 900 c.c. of slightly bloody fluid were removed. A chest roentgenogram at this time showed a small amount of fluid in the left costophrenic sinus and a residual pneumothorax at the left base. The lung fields were clear. On discharge nine days later, or 19 days after his admission to the hospital, the patient felt well, his temperature was normal, and his red cell count and hemoglobin had risen to 5,470,000 and 14.6 grams respectively.

A roentgenogram taken five weeks following his discharge showed complete re-expansion of the left lung, a clear costophrenic sinus, and normal lung fields. Since this time the patient has worked steadily and has felt well, but he still notices occasional twinges of pain in the left lower chest on deep respiration or during activity involving the musculature of the chest wall.

Case 2 This patient, a 17 year old white boy, was first admitted to Cleveland City Hospital on January 11, 1940, complaining of severe pleuritic pain in the right chest of three days' duration. A roentgenogram of the chest taken the day before admission revealed a pneumothorax on the right side with about 15 per cent collapse of the lung. There was no fluid present, and no emphysematous bullae were seen. The lung fields showed no abnormalities. The pleuritic pain subsided with rest in bed and the patient was discharged 11 days following admission. A roentgenogram of the chest taken one month later showed that the right lung had completely re-expanded.

The patient was readmitted on October 18, 1940. Since his discharge he had felt well, but several attacks of "gurgling" in his right chest, associated with mild dyspnea, had occurred, each lasting several days. Three days before admission he developed moderate pain in his lower left chest and mild dyspnea. Both became progressively worse. On admission the patient appeared undernourished and ill. The pain and dyspnea were of moderate severity. His temperature was 37.7° C, pulse 110, respirations 24, and blood pressure 120 mm Hg systolic and 80 mm diastolic. The expansion of the left chest was limited. The percussion note was hyperresonant laterally and anteriorly on the left, and dull at the left base. The breath sounds were diminished in the upper left chest and absent at the base. No râles were heard. The heart was displaced slightly to the right. The patient's hemoglobin was 12 grams, red cell count 4,700,000, and white cell count 25,250.

A clinical diagnosis was made of spontaneous pneumothorax with effusion, probably spontaneous hemopneumothorax. This was confirmed by fluoroscopy.

Diagnostic aspiration revealed the presence of gross blood having a red cell count of 357 million. A roentgenogram of the chest taken the following morning showed a spontaneous hydropneumothorax on the left with about 25 per cent collapse of the lung. The apex was adherent and the apical pleura thickened. A fluid level was present at the eighth rib posteriorly. The mediastinum was not displaced. Intrapleural pressures varied between minus two and minus 10 centimeters of water.

Subsequent fluoroscopy and examination showed no evidence of further bleeding. Removal of the blood was delayed. Nine days following admission thoracentesis yielded 650 c.c. of blood having a red cell count of 1,000,000. Four days later a second thoracentesis yielded 1000 c.c. of sanguineous fluid having a red cell count of

150,000 Two weeks after admission the lung had entirely reexpanded, but the left diaphragm was slightly higher than the right, and the left costophrenic sinus was obscured. A roentgenogram one week later showed complete clearing of the left costophrenic sinus. The patient was discharged on November 10, 1940, 23 days following admission.

Case 3 The patient, a 21 year old truck driver, was admitted to Cleveland City Hospital January 4, 1935. For two weeks prior to admission he had a cold and cough, and on one occasion expectorated about one ounce of blood. The night before admission he had a slight pain in his left chest and felt weak and dizzy. On arising from bed at 11 a.m. on the morning of admission, he developed severe pain in his left chest, and a shaking chill. Following this he noticed a hacking cough, and breathing was painful.

His temperature on admission was 38° C. He appeared acutely ill and was breathing rapidly and painfully. Examination revealed splinting of the left side of the chest, dullness to percussion at the left base, with vocal fremitus diminished below the nipple line. An area of tubular breath sounds was present at the upper level of this area in the anterior and posterior axillary lines. The mediastinum was displaced to the right, as indicated by the position of the heart. The red cell count on admission was 3,770,000, hemoglobin 80 per cent and white cell count 19,500.

The clinical diagnosis was spontaneous pneumothorax on the left with an associated effusion.

A roentgenogram of the chest taken three days after admission showed a partial pneumothorax on the left, with a dense shadow having a sharply demarcated upper border occupying the lower two-thirds of the left lung field. The mediastinum was displaced to the right. Thoracentesis was done, and 200 c.c. of gross blood were removed from the left pleural cavity. A tuberculin test done with 1:1000 dilution of old tuberculin was positive.

The patient showed gradual symptomatic improvement, and no attempt was made to remove the large quantity of blood which remained. He was discharged January 22, 1935, 18 days following his admission. A chest film taken two weeks after his discharge showed complete reexpansion of the left lung, a small amount of fluid still remaining in the left costophrenic sinus, but no evidence of infiltration of the lung fields. There were large calcified nodes present in both hilum regions. Three months later a roentgenogram of the chest showed the left costophrenic sinus to be entirely clear and the lungs to be normal.

The patient was recently examined again, after a lapse of six years. In the interim he had felt well and had worked steadily as a truck driver. A recent chest film showed no evidence of retraction of the left chest or of pleural thickening. The left costophrenic sinus was clear, and there was no evidence of parenchymatous infiltration of the lung fields.

The following discussion concerns only those cases of hemopneumothorax without apparent cause, and consequently excludes those cases following trauma and those associated with recognized active tuberculosis and malignancy, in which a cause for the bleeding is evident. A distinction is also drawn between true extravasation of blood into the pleural space and those conditions wrongly termed hemopneumothorax in which the effusion is merely blood-tinged.

HISTORICAL.

Two articles appearing together in the Transactions of the Clinical Society of London for 1660 are so complete that little of crucial importance

has been said since Pitt,¹ the first of the two authors, comments that "hemopneumothorax is an extremely rare lesion, there is no reference to it in the Index-Catalogue of the United States Library, nor is it discussed in any of the standard treatises on medicine in either English, French, or German" He presents the case of a boy 18 years old, in whom the sudden onset of pain in the right shoulder and chest was followed by the development of signs of pneumothorax with effusion on the right side associated with profound shock Insertion of a Southey tube in the right axilla resulted in the discharge of both blood and air, but despite this treatment the patient died "At the inspection about eight pints of fluid blood, and enough clot to fill the hands three times, together with a considerable amount of air under great tension, were found to occupy the right pleura The right lung was tightly compressed, and the left base slightly so posteriorly The lungs were absolutely healthy, with the exception of a small projecting emphysematous bulla, about half an inch across, near the right apex, the wall of which was imperfect, and attached to this was a fibrous band, of the thickness of a knitting needle, which had been torn across The blood may have come from a vessel in this adhesion, but no aneurysmal pouch or obviously patent vessel could be seen"

Rolleston² presented the chief clinical variant of the condition, namely, hemopneumothorax with abdominal symptoms so severe as to simulate an acute abdominal catastrophe His patient, a man 21 years old, was suddenly seized with intense pain in the right side of his abdomen, radiating to his right shoulder and to the umbilicus On admission to the hospital he was in a state of collapse and was considered to have generalized peritonitis following perforation of a duodenal ulcer Laparotomy was avoided only because death seemed imminent Two days later the patient was somewhat improved, there were signs of pneumothorax on the right side, and insertion of a trocar revealed the presence of air and blood in the right pleural cavity The patient died rather suddenly five days later At autopsy 60 ounces of dark fluid blood together with a few ounces of clotted blood were present in the right pleural cavity There were no pleural adhesions nor lung disease, nor was a source of bleeding evident A similar lack of significant autopsy findings is noted by later observers

INCIDENCE

Spontaneous hemopneumothorax is an uncommon condition Frey,³ in a review of the literature in 1935, was able to discover only 13 reported cases Of these, only 10 were truly spontaneous The remaining three were associated with recognized tuberculosis, one of the three in association with artificial pneumothorax Since that time many additional cases have been reported The largest series published to date is that of Louria,⁴ who reported five cases

In compiling cases reported in the literature, only those reports were included which were examined personally, and only those in which tubercu-

losis could be excluded satisfactorily as the cause of the condition. Within these limits we have discovered reports of 40 cases in the literature, which, with the addition of the three cases observed at Cleveland City Hospital, makes a total of 43 cases.

Examination of these 43 cases reveals a striking constancy in the age and sex incidence of the idiopathic lesion. With the single exception of a case reported by Hopkins,⁵ all the patients observed have been men. Unless due to the greater activity of men as compared to women, the explanation for this is obscure.

The age incidence of the lesion is equally constant. The age of the patient is indicated in 41 of the 43 cases. Of these, 36, or all but five, occurred in persons between the ages of 20 and 40 years. Three of the five remaining cases occurred in persons 15 to 20 years old, and the two others in persons between the ages of 40 and 45 years.

The lesion involved the left side of the chest slightly more frequently than the right, 24 of the 43 cases involved the left side, and 19 cases involved the right side. This difference is probably not significant. Of the 14 fatal cases, nine occurred on the right side and five on the left.

PATHOGENESIS

The present concept of the origin of benign spontaneous pneumothorax is that it results from the rupture of a valve vesicle situated on or near the pleural surface. These vesicles are rarely found in routine autopsies, according to Kjaergaard,⁶ they occurred approximately once in 350 autopsies in his material. Their morphology has been studied by Fischer and by Hayashi.⁷ They are thin-walled structures which may occur either as a sequel to the cicatrization of healed tuberculosis or as manifestations of localized emphysema. They communicate with neighboring bronchioles by means of a valve-like mechanism which permits the easy entrance of air but hinders its exit. The valve may consist of deformed atrophic lung tissue or may be due to bronchiolar constriction resulting from localized inflammatory processes. Because of this valvular action, the vesicle gradually becomes inflated and dilated and may rupture either as a result of exertion or during the course of normal respiratory movements. Vesicles have been observed at the autopsy table in some fatal cases of spontaneous pneumothorax and have been demonstrated radiologically in the living subject by Gordon⁸ and others.

Other explanations of spontaneous pneumothorax are not wanting. Kirsner⁹ has asserted that idiopathic pneumothorax may be the result of a congenital pleural defect and that pleural blebs are formed as a manifestation of a primarily weakened pleura. Hamman¹⁰ has observed pneumothorax in two of seven cases of spontaneous mediastinal emphysema and thinks that it is due to rupture through the thin mediastinal wall permitting the escape of air into the pleural cavity. Kirsner, in a later article,¹¹ advances the

explanation that pneumothorax may be due to the rupture of pleural bullae formed secondary to a localized interstitial subpleural emphysema resulting from the rupture of an alveolus or terminal bronchiole with the escape of air into the interstitial tissues

Evidences that ruptured bullae are significant in the causation of hemopneumothorax are, first, their frequent occurrence in autopsied cases of hemopneumothorax, second, the roentgenologic demonstration of bullae in non-fatal cases, and third, the successive occurrence of spontaneous pneumothorax and hemopneumothorax in the same patient. The autopsy findings in cases of hemopneumothorax are given below. Undoubted bullae have been demonstrated roentgenologically in at least two cases of spontaneous hemopneumothorax, those of Castex and Mazzei,¹² and of Troisier, Bari  ty, and Dugas.¹³

The second of the Cleveland City Hospital cases represents one in which a spontaneous pneumothorax was followed within the year by spontaneous hemopneumothorax on the contralateral side. Rist¹⁴ reported the case of a young Chinese student in whom a spontaneous pneumothorax of the idiopathic variety associated with a small amount of hemorrhagic fluid was followed almost two years later by a spontaneous pneumothorax on the same side. Rossel¹⁵ has described an autopsied case of massive idiopathic hemopneumothorax which was suddenly fatal owing to the development of contralateral pneumothorax five days later. In the case reported by Palmer and Taft,¹⁶ spontaneous pneumothorax was preceded by two years by the development of a contralateral hemothorax of unknown etiology.

AUTOPSY FINDINGS IN 14 CASES OF FATAL HEMOPNEUMOTHORAX

The autopsy findings in 14 published cases of fatal hemopneumothorax are as follows:

1. Pitt¹ discovered a ruptured emphysematous bulla at the apex of the involved lung, to which was attached a torn adhesion. He suggested that the bleeding may have come from a vessel in the adhesion. A patent vessel was not seen.

2. Rolleston² found no lung disease, pleural adhesions, or source of bleeding.

3. Fischer's case¹⁷ presented bilateral areas of localized emphysema and scarring due to healed pulmonary tuberculosis at both apices. On the side of the hemopneumothorax there was observed a large vesicle covered with coagulated blood, from which fresh blood oozed on pressure.

4. Kiaer's patient,¹⁸ as summarized by Perry,¹⁹ showed no significant pathologic change either in the lung or on the pleural surface.

5. Housden and Piggot's case²⁰ revealed a small puckered tuberculous scar at the apex of the involved lung, multiple discrete and coalescent emphysematous bullae, and also two torn apical adhesions. No source of

bleeding or site of rupture of the lung was found, but the authors felt that the abnormalities found probably explained both the escape of air and the bleeding

6 Davidson's first case ²¹ disclosed contralateral adhesions and a small tuberculous scar. On the side of the hemorrhage, however, no lesions were found, nor was the source of the bleeding identified

7 In the second case of Davidson ²¹ delicate vascularized adhesions were present associated with a chronic bronchopneumonia. It was assumed that these were the source of the escaping blood

8 Rossel's case ¹⁵ was one of hemopneumothorax with death due to the development of contralateral pneumothorax five days later. On the side of the bleeding, a pea-sized thick-walled umbilicated bulla was found within an area of tissue induration, but the site of escape of blood and air was not determined. On the contralateral side, a ruptured subpleural bulla was found

9 Tait and Wakeley ²² report an autopsied case showing, on the side of the bleeding, a series of about 12 bullae in and near the apex, ranging, when distended, up to the size of a small cherry. One of these had perforated, and the aperture was filled with recent blood

10 Jones and Gilbert ²³ found in their case an emphysematous cavity 1 cm in diameter at the apex of the involved lung, but no communication between this cavity and the pleural space, no adhesions, and no source of bleeding were observed. Organizing fibrin masses were present, which constricted the mediastinum and which were presumed to have caused death from circulatory obstruction

11 Louria's case ⁴ showed a ruptured emphysematous bleb in the interlobar sulcus of the homolateral lung, without evidence of a source of bleeding. The contralateral lung showed healed tuberculosis, a few adhesions, and emphysematous blebs

12 The autopsy on Perry's case ¹⁹ revealed on the side of the bleeding fibrous adhesions extending between the upper lobe and the parietal pericardium. Hemorrhagic infiltration was present in these adhesions, but the actual bleeding point was not identified, nor was a perforation of the pleura discovered. Intact bullae, subpleural fibrosis, and other adhesions were also present

13 Davidson and Simpson ²⁴ discovered a ruptured bulla at the apex of the involved lung. They also observed blood issuing from a small band of adhesions at the corresponding base. There was a small apical tuberculous scar. They concluded that collapse of the lung resulting from rupture of the apical bulla had stretched and torn the adhesions at the base, and that slow but continuous bleeding from these adhesions was responsible for death

14 Lorge's case ⁷ showed slight scarring and a few emphysematous bullae at the apex of the involved lung. However, the pleural surface was everywhere intact, and no source of bleeding was found.

In summary, a survey of the autopsied cases of hemopneumothorax reveals that in most instances the source of bleeding is not clearly identified. Torn adhesions and ruptured bullae have been implicated in some of the cases. Mazzei and Pardal²⁶ have shown that, contrary to the usual conception, subpleural bullae may be richly vascularized. They have demonstrated in the lining of the bullae a layer of new formed vessels with abundant communicating anastomoses, which could well give rise to significant intrapleural hemorrhage. The second possibility is that adhesions torn by the traction of the collapsing lung are responsible for the bleeding. Leopold and Lieberman²⁷ found adhesions at autopsy in almost 50 per cent of all persons above the age of 20, after eliminating those cases with a history of acute or chronic pulmonary disease. The vascularity of adhesions is well known to the thoracic surgeon, and bleeding from adhesions is the more sinister since their blood supply, according to Matson,²⁸ is derived largely by collaterals from the intercostal vessels. Bleeding may occur as a result of complete rupture of the adhesion or as a result of a tear at the base of an adhesion still retaining its attachment to the visceral pleura.

To determine whether the hemorrhage in a given case is parietal or pulmonary in origin is nearly impossible. Since adhesions of parietal vascularization carry an arterial pressure which is six times that of the pulmonary circuit, ruptured adhesions seem to explain most satisfactorily the source of massive intrapleural hemorrhage. Moreover, the collapse of the lung should usually stop hemorrhage arising from subpleural bullae, whereas it would exert no hemostatic action on bleeding from torn adhesions. Hemorrhage from intercostal arteries is noted for its severity, but these can be implicated only indirectly in spontaneous intrapleural bleeding.

The duration of time required for the pleural space to fill with blood is also of interest. In most cases of hemopneumothorax which do not prove fatal, the bulk of the bleeding has already occurred when the patient is first seen. Rist and Worms,²⁹ however, observed a case in which signs of dry pneumothorax were followed 12 hours later by evidence of extravasation of blood. I have seen a massive pleural hemorrhage following a pneumothorax refill develop over night when, 12 hours following the refill, the quantity of blood present as seen fluoroscopically was insignificant. The occurrence of slow but cumulative intrapleural bleeding lends plausibility to the contrast between the massiveness of the extravasation of blood and the apparent insignificance of its source.

TUBERCULOSIS AND OCCULT CAUSES OF HEMOPNEUMOTHORAX

The manifest causes of hemopneumothorax are beyond the scope of this discussion. Hemopneumothorax in tuberculosis usually occurs when the disease is both obvious and advanced. Consequently, cases in which tuberculosis is not obvious or easily discovered at the time of the episode of bleeding may confidently be considered non-tuberculous. Millhorat³¹ re-

ported a six and one-half year follow-up of a case of hemopneumothorax. The roentgenogram showed a shallow costophrenic angle on the side of the previous lesion, with pleural thickening and irregular calcification in the lower lateral lung field. It also showed some thickening of the apical pleura, which Milhorat interpreted as indicative of an old apical tuberculous lesion. There was no evidence of active disease.

Two exceptions may be noted to the rule that tuberculosis causing hemopneumothorax is both advanced and obvious. Beatty³¹ has reported the case of a colored man 20 years old who at the time of his hemopneumothorax had no infiltration in the homolateral lung and only a small amount of apical infiltration in the contralateral lung. Four months later the patient developed frank cavitating tuberculosis in the contralateral lung, and his sputum was positive for tubercle bacilli. This was treated by pneumothorax with improvement. Birch³² observed a fatal case of hemopneumothorax in which autopsy disclosed a minute tuberculous cavity at the apex of the involved lung. There was no evidence of tuberculosis elsewhere. The source of escape of blood and air was not certainly identified, but appeared to be a roughened area on the pleural surface, since the cavity wall was intact.

Hemopneumothorax is uncommon even in frank advanced pulmonary tuberculosis. Lung collapse in the presence of advanced pulmonary disease is far more apt to result in pyopneumothorax than in intrapleural bleeding. Heise and Krause³³ reported a fatal case occurring in a man with rapidly progressive caseous tuberculosis, developing after his first pneumothorax treatment. Intrapleural bleeding following pneumothorax refills has been reported, and we have observed two such patients during the past year at Cleveland City Hospital. One of the patients made a complete clinical recovery, the other, some weeks following his episode of intrapleural bleeding, developed a spontaneous collapse of the lung on the same side which resulted in mixed infection empyema. Weiner and Jackson³⁴ have reported the occurrence of spontaneous bleeding and collapse of a lung under treatment by artificial pneumothorax in a tuberculous patient who had had a thoracoplasty on the contralateral side.

It is at first thought surprising that hemopneumothorax does not occur more often as a complication of manifest pulmonary tuberculosis. Korol³⁵ provides a partial answer to this question. In the first place, lung perforation involves the periphery of the lung where the blood vessels are small, and tuberculous lung tissue, the seat of the perforation, is characteristically poor in blood supply. In the second place, the collapse of the lung which results from pleural perforation brings about a retraction of the injured blood vessels and mechanically tends to stop bleeding.

Among the occasional occult causes of spontaneous intrapleural bleeding, Jacob³⁶ has reported a case of spontaneous hemopneumothorax in a young man with a history of hemoptysis and expectoration since childhood. Clinically he was considered to have bronchiectasis, but the diagnosis was not confirmed by bronchograms.

Malignancy involving the pleura gives rise commonly to a bloody effusion, but less frequently to the escape of frank blood. Hemothorax due to malignancy is not accompanied by the escape of air into the pleural space.

THE CLINICAL PICTURE

The picture of idiopathic hemopneumothorax is that of an acute illness, and the most striking and most constant early symptom is pain. In some cases an initial period dominated by pain is followed by a latent period of apparent improvement, and this is then followed by evidence of shock and collapse resulting from intrapleural bleeding and mediastinal displacement. In occasional cases the onset of the pain is associated with coughing, straining, lifting, or some other exertion altering the intrapleural pressure.

The initial pain is usually sudden in onset, sharp, stabbing, and continuous in character, localized to the side of the chest which is involved. The pain may remain localized, but not uncommonly radiates to the shoulder of the involved side, and, significantly, frequently radiates to the abdomen. Dyspnea in some degree usually appears immediately or after an interval. Nausea, vomiting, and even diarrhea are not uncommon. Shock, anemia, signs of collapse and of internal hemorrhage follow in the more severe cases. The physical findings are those of pneumothorax with effusion, and the chest film is diagnostic of hydropneumothorax. The laboratory findings are not characteristic. An anemia develops which is proportional to the extent of intrapleural bleeding. A moderate leukocytosis is usually present.

Finally, a few helpful diagnostic hints may be mentioned. First, the association of signs of hydropneumothorax with those of anemia and internal hemorrhage, coupled with a clinical history of short duration, permits the diagnosis of hemopneumothorax. Second, an effusion appearing within a few hours in a pneumothorax space either artificial or of spontaneous origin is almost certainly blood, for a serous effusion develops only after a pleural reaction lasting one or several days. Third, excluding tuberculosis, the other causes of massive intrapleural bleeding do not at the same time produce pneumothorax. Thoracentesis will quickly determine the nature of the fluid present. In doubtful cases, it is advisable to do a red cell count on the fluid withdrawn, to make sure that it is largely blood and not merely bloody exudate.

Hemopneumothorax with signs referred to the abdomen constitutes the chief clinical variant of the condition. The combination of right upper quadrant pain, shoulder pain, and nausea and vomiting, with occasionally obliteration of liver dullness, has proved especially confusing. The explanation for the abdominal pain is to be found in the common innervation of the lower parietal and diaphragmatic pleura and the abdominal viscera by sympathetic nerves connecting with the lower six thoracic segments of the cord. Exploratory laparotomy was performed in the case reported by Fischer,¹ and was avoided by Rolleston only because his patient seemed

moribund Grabfield³⁷ has reported a case simulating acute appendicitis, and abdominal symptoms were prominent also in the cases reported by Hurxthal³⁸ and Milhorat³⁹ The patient reported by Rist and Woims²⁹ was first suspected of coronary occlusion

THE STATE OF THE BLOOD IN THE PLEURAL CAVITY

Aspiration in cases of hemopneumothorax yields dark fluid blood, and at autopsy the majority of the pleural blood is unclotted The fluidity of the blood has been observed not alone in spontaneous hemopneumothorax, but also in pleural bleeding of traumatic and other origin According to Sacquepee, blood in the pleural space becomes incoagulable after contact with the pleural membranes for four to five hours in man, after two hours in the dog This is true only if the pleura is not infected Consequently, the discovery of clotted blood when performing thoracentesis means either that bleeding has not yet stopped, or that infection has taken place

The probable explanation of the incoagulability of blood in hemothorax originates with Trousseau According to this author, blood actually clots rapidly in the pleural cavity, even more rapidly than in external hemorrhage As a result of agitation produced by cardiac and respiratory movements, the blood is rapidly defibrinated and the fibrin deposited on pleural surfaces before the red cells have had time to precipitate Massive deposition of fibrin on pleural surfaces and surrounding the mediastinum was observed in the autopsied case of Jones and Gilbert, and these authors attributed the death of their patient to circulatory obstruction resulting from the contraction of organizing fibrin masses In other autopsied cases, fibrin masses have not been found

Eosinophilia is frequently observed in the intrapleural blood and its serous diluent during the process of resorption Eosinophilia in pleural effusions is discussed by Grabfield³⁷ The explanation of Klein, that the eosinophiles represent neutrophiles which have engulfed hemoglobin from red cells, appears improbable, in his opinion

COURSE AND PROGNOSIS

Fourteen of the 43 cases, or approximately one case in three, terminated fatally This figure doubtless exaggerates the mortality of spontaneous hemopneumothorax, both because authors have been more ready to report autopsied cases and because especial care has been taken to include reports of autopsied cases in this discussion

Of the 14 fatal cases, satisfactory data are available concerning the time of death of 11 cases Of these 11, five died within 24 hours of their admission to the hospital four additional patients died within a week, and in two cases death occurred after more than a week in the hospital One of the latter two died after 28 days in the hospital, apparently of mediastinal obstruction due to organizing fibrin masses Earlier deaths are due to shock,

anemia, and respiratory and circulatory embarrassment associated with mediastinal displacement

The escape of blood into the pleural space evokes an inflammatory response manifested by fever, pleuritic pain, and reactive serous effusion. The serous effusion subsides gradually with repeated tapping. The occurrence of empyema following spontaneous hemopneumothorax is a rarity.

TREATMENT

The treatment of idiopathic hemopneumothorax is based upon several considerations. In the first place, the pneumothorax and the positive intrapleural pressure are probably beneficial to the extent that they tend to stop bleeding. On the other hand, the mediastinal displacement, a result of the positive intrapleural pressure, is harmful when present to the extent that it embarrasses the circulation and respiration. The physician is, therefore, impelled both to withdraw the blood and to do nothing, and his decision will depend upon the time of the illness at which he sees the patient, the degree of mediastinal displacement, and the probability that the bleeding has stopped. A third consideration which will influence his treatment is the possibility that the blood is obscuring tuberculous infiltration of the lung parenchyma and his desire to maintain the pneumothorax artificially until he can be certain of the integrity of the underlying lung tissue.

If the patient is seen soon after the onset of the illness, only enough blood should be removed for diagnostic purposes, provided the mediastinal displacement is not sufficient to cause distressing dyspnea or to embarrass the circulation. Delayed removal of the blood may then be performed, and air injected sufficient to prevent too sudden an alteration of the intrapleural pressure and to maintain the pneumothorax if it is desired to do so.

Shock when present must be treated. Infusions and transfusions are resorted to with reluctance dictated by the possibility that they may initiate fresh bleeding. Withdrawal of the pleural blood and its re-infusion into the patient's veins has been advocated by Rossi, and practiced by Brown and Debenham⁴⁰ in cases of traumatic hemothorax. The procedure is doubtless safe, but seems unnecessary in view of the simplicity of modern transfusion technique.

In the more serious cases improvement fails to occur with these medical measures, and fluoroscopic observation of the level of fluid in the pleural space provides evidence that the bleeding continues. Open operation in an attempt to find the bleeding point may then be considered if a hardy surgeon is available. There is no report of attempted operative treatment of spontaneous hemopneumothorax among the cases which we have compiled.

SUMMARY

Three cases of idiopathic hemopneumothorax have been presented, and the literature has been reviewed briefly. The condition is seen in healthy

young men without a history of previous lung disease. Clinically it presents in rapid sequence the onset of chest pain followed by dyspnea, anemia, and shock associated with mediastinal displacement. Its physical findings are those of hydropneumothorax at times associated with confusing abdominal signs. Its pathogenesis is not entirely clear, but some cases are known to develop when spontaneous pneumothorax resulting from rupture of an apical bulla is complicated by the tearing of pleural adhesions during the course of the collapse of the lung. Treatment consists of rest, thoracentesis with or without the introduction of air, and possibly surgical intervention when necessitated by continued bleeding. The condition has no relation to active tuberculosis, and the prognosis, provided the patient survives the acute episode, is good.

The Cleveland City Hospital Cases are presented through the courtesy of Dr. R. W. Scott, Director of the Department of Medicine of the hospital.

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Addendum. Since this paper was submitted for publication, an additional case of spontaneous hemopneumothorax has been seen at Cleveland City Hospital. The patient was a white male 22 years of age, and the right side was involved. Thoracentesis performed two and three weeks after the onset yielded 1000 cc of blood and 650 cc of bloody fluid respectively. His convalescence was uneventful and roentgenograms of the chest failed to reveal lung disease.

His past history was significant in that it disclosed an episode of chest pain and dyspnea appearing following heavy lifting two years prior to the development of hemopneumothorax, strongly suggestive of the previous occurrence of spontaneous pneumothorax on the homolateral side. He was not studied roentgenologically at that time, and the association of spontaneous pneumothorax and spontaneous hemopneumothorax therefore remains unproved in this case.

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BACTERIAL ENDOCARDITIS AND CONGENITAL HEART DISEASE (WITH REPORT OF TWO CASES) *

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THE purpose of this paper is to present two interesting cases of congenital heart disease terminating fatally with the development of bacterial endocarditis. The first case, that of bacterial endocarditis superimposed on a bicuspid aortic valve, illustrates the devastating effects produced by this combination of lesions, the second, that of bacterial endocarditis superimposed on the margins of a ventricular septal defect, presents the exceedingly rare situation of an acquired complete auriculo-ventricular dissociation related to the endocarditis.

CASE REPORTS

Case 1 A 36-year-old white man, prematurely gray, was admitted to the medical service of the Roosevelt Hospital on January 21, 1940, complaining of fever and chills of one week's duration. Past history was essentially negative. He was acutely ill, with a rectal temperature of 104° F. The pharynx appeared reddened. The lungs were clear. The heart was not enlarged, there was regular sinus rhythm. A soft apical systolic murmur was noted. Blood pressure was 120 mm Hg systolic and 80 mm diastolic. The spleen was just palpable under the left costal margin. There were no meningeal signs. No rash was noted. There was a slight leukocytosis, and a slight secondary anemia. Roentgen-rays of the lungs and heart were negative. Three days after admission small macular spots appeared on the skin of the anterior chest. The systolic murmur previously heard became harsher and louder. Conjunctival, palatal and retinal hemorrhages appeared. Because of the development of slight stiffness of the neck and a questionable Kernig sign, a spinal puncture was done. The fluid removed was normal in all respects. The next day a diastolic murmur, best heard in the third left intercostal space, became audible. A blood culture was then reported positive for *Streptococcus viridans*. Eight days after admission the right radial pulse became markedly reduced in volume. This suggested embolic occlusion of this vessel. At this time there appeared painful areas on the fingertips having the characteristics of Osler nodes, petechial hemorrhages over the heads of the metacarpals (palmar surface), and Janeway spots (palms). Several days after the reduction in the volume of the right radial pulse there appeared, just below the bend of the right elbow, a very circumscribed area of pulsation. Several days later the patient developed a right hemiplegia. After this the course was rapidly downward, being characterized by spiking temperature and increasing signs of toxicity and stupor. Just before death a pericardial friction rub was noted. The patient died three weeks after admission. Permission was obtained for autopsy, excluding examination of the cranial contents.

Summary of Autopsy Findings The pericardial cavity contained about 200 c c of turbid, reddish brown, bloody fluid. Its lining was roughened with fibrinous exudate. Hemorrhages studded the anterior surface of the pulmonary conus. The

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heart was slightly enlarged, the ventricles considerably dilated. The myocardium was brown and flabby, but free of fibrosis. The posterior wall of the left ventricle over an area measuring 3 by 5 cm in its entire thickness was necrotic, and gray-green in color. Its midportion was thinned out, measuring 5 mm in contrast to the wall at the base which was 15 mm thick. There was no mural thrombosis. The aortic ostium was narrowed by a large vegetation which measured 2 cm from side to side and 3 cm from above downward. It was 1 cm thick (figure 1). Its surface was uneven and



FIG. 1 Heart showing large aortic vegetation, embolus in coronary artery and myocardial infarct

Microscopic Examination The aortic vegetation was made up of fresh and necrotic fibrin with dense focal accumulations of polymorphonuclear leukocytes. Gram stains revealed gram-positive cocci deep in the substance of the vegetation. The myocardium showed necrosis of muscle fibers and acute myocarditis. No bacteria were noted in the myocardium. The wall of the radial artery was necrotic and infiltrated with polymorphonuclear leukocytes. The pericardium showed beginning organization of an acute fibrinous pericarditis.

Anatomic Diagnosis Bacterial endocarditis of aortic valve (bicuspid)—*Streptococcus viridans*. Embolic occlusion of right coronary artery with infarction of posterior wall of left ventricle. Embolic occlusion of right radial artery with necrosis of its wall. Hemorrhagic fibrinous pericarditis with effusion. Dilatation of both ventricles. Multiple splenic, renal and suprarenal infarcts. Chronic passive hyperemia of lungs, liver, kidneys, stomach, intestines. Bilateral apical pleural scars. Fibrous adhesions right pleural cavity. Purulent bronchitis. Pulmonary edema. Caseation of tracheobronchial lymph glands. Acute follicular hyperplasia of spleen.

Case 2 A case of probable *Staphylococcus albus* endocarditis superimposed on the margin of a ventricular septal defect and aortic valve. An 18-year-old white boy was brought to the Roosevelt Hospital by ambulance on September 18, 1939, with the history of recurrent drenching night sweats and syncope. En route he vomited several times and in the Reception Ward had several recurrences of syncope. In the past it had been noted that he had frequent nose-bleeds and an occasional sore throat but no history of rheumatic fever or its equivalents could be elicited. There was a history of "leaky valves." There were past episodes of precordial pain, ankle edema and dyspnea. On physical examination moderate elevation of temperature was noted. The heart was slightly enlarged. The rhythm was irregular, the rate about 20 per minute. There was a loud systolic murmur heard best to the left of the sternum over the pulmonic area. Blood pressure was 94 mm Hg systolic and 76 mm diastolic. Spleen could not be palpated. Liver was just palpable at costal margin. Testicles

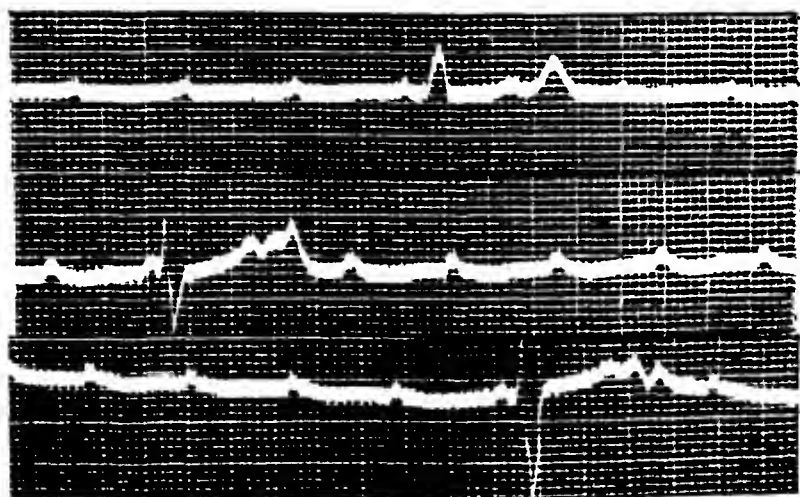


FIG 2 Electrocardiogram showing complete A-V dissociation. Leads I, II, III, from above downward.

were in the inguinal canal. Urine showed a trace of albumin. Hemoglobin and erythrocyte values were normal. Slight leukocytosis was present. Blood urea was 21.0 mg per 100 c.c. blood. Several of numerous blood cultures showed *Staphylococcus albus*. Widal was negative. Roentgen-ray showed the heart to have a globular con-

tion and to be slightly increased in the transverse diameter with enlargement predominantly of the left ventricle. Electrocardiogram on day of admission showed complete auriculoventricular dissociation. The auricular rate was 123 and the ventricular rate was about 16 (figure 2). A diagnosis was made of congenital heart disease, probable ventricular septal defect, complete heart block, Adams-Stokes syndrome, probable subacute bacterial endocarditis. On admission and for several days thereafter he received numerous injections of adrenalin and atropine with occasional increase in pulse rate, though without restoration of normal sinus rhythm. He was then given injections of adrenalin-in-oil, 1 cc every day for five days without effect on the rhythm. On the sixth day, in addition to the injection of adrenalin-in-oil he received barium chloride 0.060 gm. On the seventh day he received adrenalin-in-oil and barium chloride, 0.120 gm. For the next three days barium chloride was given without adrenalin, in doses of 0.060 gm, 0.060 gm, and 0.030 gm respectively. On the third day after the barium was started the electrocardiogram showed a regular sinus rhythm (figure 3). During the fourth week after admission several chills with

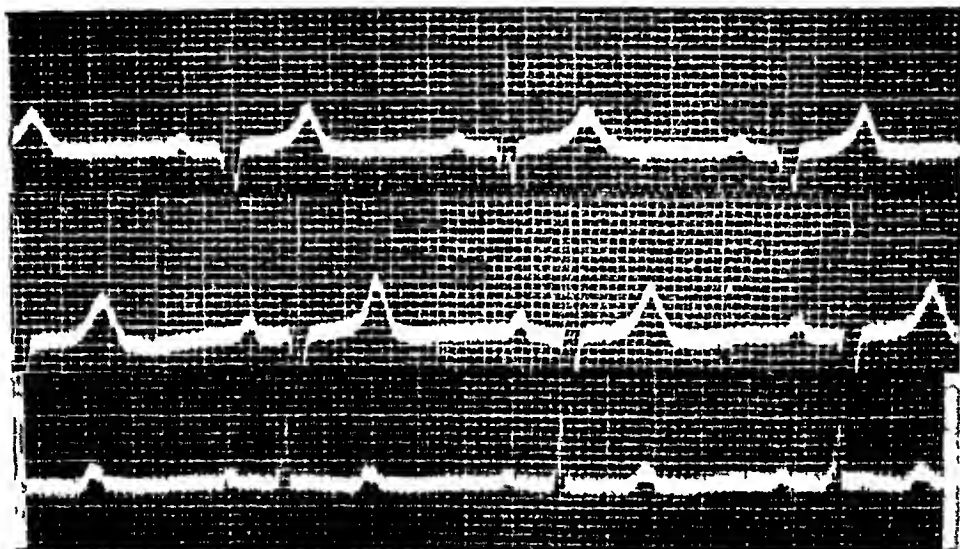


FIG 3 Electrocardiogram showing normal sinus rhythm

temperature spiking to 106° F were noted. Spleen became palpable and soon after that it was noted that the tip of the right index finger was tender. From this time until his death, three weeks later, his course was characterized by spiking temperature and chills. Just before his death a loud blowing diastolic murmur was noted for the first time over the precordium. Permission was obtained for autopsy excluding examination of the brain.

Summary and Findings The heart weighed 500 gm. The interventricular septum presented a rounded defect at the base measuring 4 mm in diameter (figure 4). The surrounding endocardium was smooth and glistening on the side of the right ventricular chamber, but on the left side one noted along its anterior margin a firm, pink vegetation which measured 1 by 2 by 1 cm. It was not easily separated from the underlying endocardium. The cusp of the aortic valve situated immediately above the vegetation revealed a perforation approximately 3 mm in diameter. The remaining aortic cusps were normal in appearance and number. The aortic valve measured 7 cm.

Microscopic Examination Sections through the myocardium revealed slight fibrosis, some hypertrophy of muscle fibers, and slight brown pigmentation. Section

through the margin of the defect to which the vegetation was attached revealed the latter to be made up of homogeneous, pink-staining, finely granular material, with interlacing strands of fibrin and scattered polymorphonuclear leukocytes. The margin of the defect to which the vegetation was adherent consisted of a central core of dense connective tissue, rather poor in cells, flanked on both sides by a layer of granulation tissue, rich in thin-walled capillaries, and fibroblasts, with scattered polymorphonuclear leukocytes and mononuclear cells. Sections through a block of tissue cut from the upper margin of the septal defect and carried for a centimeter upward to



FIG 4 Heart showing ventricular septal defect, a large vegetation on the defect-margin aortic valve leaflet

include the auricular septum showed the cardiac muscle to be made up of bundles of fibers separated by dense connective tissue in which cells were very rare. A small amount of connective tissue separated the individual muscle fibers. These fibers appeared usual in structure. The cell-poor connective tissue appeared focally hyalinized. Just above the septal margin was noted a discrete bundle of rather narrow fibers with dark-staining nuclei and eosinophilic cytoplasm. This was identified as the bundle of His. It exhibited fibrosis and focal degeneration of muscle fibers. The bundle was separated from the main body of interatrial myocardium by a wide zone of dense fibrous connective tissue, poor in cells, and focally hyalinized. The aortic vegetation presented the same appearance as that springing from the defect margin.

Smears from the vegetation revealed gram-positive coccil organisms. Culture of heart's blood revealed *Staphylococcus albus*.

COMMENT AND DISCUSSION

Bacterial endocarditis is a condition occurring most frequently in hearts which have been affected by rheumatic fever, and less frequently in hearts with congenital defects such as bicuspid semilunar valves, ventricular septal defect, or patent ductus arteriosus. Maude Abbott¹ points out the great danger of acute or subacute bacterial endocarditis or endarteritis developing in individuals with cardiac anomalies. She notes that fibrosed semilunar valves or the margins of septal defects are particularly vulnerable. Of 555 cases of congenital heart disease analyzed by her, 98 or 17.6 per cent presented an endocarditis. Of these, 40 per cent were in defects of the base of the ventricular septum such as presented by our second case, and 45 per cent in cases with bicuspid aortic valves, such as presented by our first case. Congenitally bicuspid aortic valves are particularly susceptible to superimposed infection as shown by Lewis and Giant² who report 11 cases of bicuspid aortic valves, seven of which showed the presence of bacterial endocarditis. In Abbott's 32 cases of bicuspid aortic valves, 13 died of acute endocarditis of which nine were bacterial. Osler³ reported 18 cases of bicuspid aortic valves, seven of which showed recent vegetations. As a rule one segment of a bicuspid aortic valve is larger than the other and often shows evidence of fusion of two segments.⁴ These points are well illustrated in our first case.

The first case presented was that of a 36-year-old white male. In Abbott's cases the average age noted was 33 years, and males predominated in proportion of 13 to 1. Wauchope⁵ in a series of 52 cases in 9966 autopsies noted a predominance of males in the proportion of 3 to 1. Though the facts that the patient had a bacterial endocarditis and that his aortic valve was involved were fully recognized, the basic nature of the valvular defect was not suspected. The importance of a correct diagnosis of the basic defect is purely academic, though it is noted that the most devastating effects are seen where bacterial endocarditis occurs on a bicuspid valve.

The occurrence of pericarditis in this case deserves brief mention inasmuch as it is quite rare as a complication of bacterial endocarditis as pointed out by Libman,⁶ and by Thayer⁷ in his exhaustive treatise on endocarditis. The latter points out that the diagnosis is rarely made clinically.

The pathogenesis of the pericarditis cannot be stated with certainty. Coronary occlusion with myocardial infarction is often accompanied by pericarditis. The infarction in our case involved the entire thickness of the wall and the pericarditis was very likely the result of this. The diffuseness of the pericarditis and the hemorrhagic exudation may have been related to the fact that the embolus was infected and to the probable presence of bacteria in the myocardium (which in the infarcted area was gray-green in color) in spite of the fact that bacterial stains failed to reveal them.

In Maude Abbott's series of 62 cases of ventricular septal defect, 50 had defects at the base of the septum as illustrated in our second case. Of these, 21 had acute endocarditis, of which 13 died of bacterial endocarditis. Fourteen showed a chronic lesion. Heart block due to or dependent upon a congenital anomaly of the heart is rare, although Yater and his co-workers,^{8, 9, 10} who have written extensively on the subject, point out that it is not so rare as formerly supposed. The acquired form of heart block on the basis of a congenital anomaly¹¹ is even rarer. Up to 1934 a careful search of the literature by Yater failed to reveal any detailed report of acquired heart block due to or directly associated with a congenital anomaly of the heart. Yater reported the first case with complete histopathologic examination. The bundle of His was smaller than normal in diameter and ran along the free edge of the interventricular septum. A short distance from its origin it became fibrotic, and Yater attributed the fibrosis to strain and not infection. The bundle in our case was fibrotic and showed focal degeneration.

The absence of a history of syncopal attacks in our case prior to the onset of the present illness and the resumption of normal sino-auricular conduction before death preclude the possibility that complete block existed prior to the present illness.

The presence of a vegetation in close proximity to the bundle would indicate the possibility of direct involvement of the bundle in the inflammatory reaction. Since the patient lived for some time after the resumption of normal conduction, all signs of inflammation could have disappeared by the time the patient died. It is also possible that because of its proximity to the vegetation the bundle may have become involved temporarily by inflammatory edema. Which of these two explanations is the correct one cannot be stated, both may have played a rôle. Presumably the barium chloride had nothing to do with the recovery from the block, though conduction along the bundle resumed soon after the administration of the drug, after repeated failure of other drugs to produce this effect. We felt that this was purely a coincidence and that the bundle of His was in some way involved in the infective process, the subsidence of which permitted the resumption of normal conduction.

SUMMARY

1 Two cases of congenital heart disease are presented in which bacterial endocarditis became superimposed on the defect and caused death.

2 One of the cases, that of bicuspid aortic valve, illustrates the devastating effects peculiar to this lesion. The unusual complication of pericarditis and its pathogenesis are discussed.

3 The other case, that of ventricular septal defect, is of exceptional interest, inasmuch as a complete auriculoventricular block developed. The bundle of His exhibited fibrosis and focal degeneration. Resumption of normal conduction occurred before death. The pathogenesis of the block is briefly discussed.

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CASE REPORTS

TUBERCULOUS SPLENOMEGALY, STUDY OF A CASE

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THE occurrence of tuberculous involvement of the spleen in the course of miliary or advanced tuberculosis of other organs is common^{1, 2, 3, 4}. However, extensive active tuberculosis localized in the spleen is rare. When this disease occurs, it usually is associated with lesions of lesser extent in the nearby lymph nodes and in the liver, but the spleen appears to be the disseminating focus. Less than 100 cases of this type of tuberculous splenomegaly are recorded. Not all of them have been studied thoroughly and in many reports the specific characteristics are difficult to evaluate.

We present a case of unusually large splenomegaly due to chronic caseating tuberculosis, together with studies which concern chiefly the hematopoietic tissues.

CASE REPORT

J M L, a white male, Swiss, 54 years of age, entered the University of California Hospital on November 8, 1935, complaining of enlargement of the abdomen, fever, sweats and loss of weight and strength. He denied any significant illness in the past. He had traveled extensively in temperate climates throughout the world carrying on his occupation of cook. His father had died of pleurisy at the age of 64 and one sibling had died of tuberculosis at the age of 14. His present illness began about eight months before entry, at which time he noted the onset of progressive enlargement of the abdomen, especially on the left side. During this interval he had three episodes of acute pain in the left upper quadrant of the abdomen which were associated with vomiting. The last episode was accompanied by fever and repeated chills, and persisted for three weeks. He had continuous night sweats and lost 20 pounds in weight.

On physical examination the patient appeared chronically ill. Numerous petechiae were scattered over the back, thighs and arms. There was a salmon-pink blush on the palms and soles. Small discrete inguinal, axillary and cervical nodes were present. Small xanthomata were noted on the eyelids. The thorax was normal and the lungs were clear. The heart was normal. Blood pressure was 110 mm Hg systolic and 70 mm diastolic. The abdomen was moderately distended with gas and fluid. The spleen was ballotable and filled the entire left side of the abdomen. Its incisura was felt opposite the umbilicus. It was smooth except for a small nodule on its anterior surface. The liver was smooth, non-tender, and extended 5 cm below the right costal margin. Dilated veins coursed longitudinally over the surface of the abdomen (figure 1). Bilateral inguinal herniae were present.

Laboratory Procedures Urine normal. Stool normal. Gastric analysis abundant free and total acid present. Blood Wassermann reaction negative. Lu-

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berculin test (with old tuberculin) human, negative, bovine, strongly positive Takata-Aia reaction strongly positive Rose Bengal test interpreted to indicate moderate impairment of liver function Plasma cholesterol 212 mg per 100 c c

A roentgenogram of the chest revealed normal lungs Biopsy of an inguinal lymph node showed no abnormality Abdominal paracentesis was done, and 36 c c of dark red fluid were removed The fluid had a specific gravity of 1.020 and contained 85,000 erythrocytes and 600 lymphocytes per cubic millimeter The Rivalta and globulin tests which were done on the fluid were positive A month later 4000 c c of dark red fluid were removed by a second abdominal paracentesis The fluid had a specific gravity of 1.022 and contained 800,000 erythrocytes and 10,000 leukocytes per



FIG 1 Infra-red photograph showing collateral venous channels

cubic millimeter Culture of this fluid did not show growth, but tuberculosis developed in guinea pigs into which it was injected The blood studies are indicated in tables 1, 2 and 3

Course and Treatment Attempts to stimulate leukopoiesis failed, as can be seen from the tables A high purine diet was given continuously Sodium nucleinate of thymus gland was administered in doses of 10 c c intramuscularly twice daily for several days Liver extract (Lederle) was given in daily doses of 3 c c intramuscularly on November 9, 10 and 11, and epinephrine in doses of 0.3 c c four times daily on November 12 and 13 Abdominal distention was controlled by paracentesis, fluid restriction, and the intravenous administration of salyrgan No lymph node enlargement developed Petechiae were constantly present, but no gross hemorrhages occurred Daily intermittent fever of 38 to 39° C persisted On January 20, 1936, the patient

was transferred to the Los Angeles County General Hospital. He pursued a steadily failing course and died rather suddenly on January 27.

Autopsy (Performed by Dr J L Mason on January 29) The abdomen was moderately distended and contained 2000 cc of turbid red fluid. The parietal peritoneum was smooth, but the visceral peritoneum was covered with thick fibrinous exudate which had accumulated in large quantities beneath the diaphragm and had formed adhesions resembling cobwebs. The left pleural cavity contained 750 cc of clear yellow fluid with a specific gravity of 1.010. The pleural surfaces were smooth. The lungs showed passive congestion but no infiltrative lesions or scars. A caseous paratracheal node measured 1.5 cm in length. The pericardium was red and shaggy.

TABLE I
Studies of the Blood

Dates	Nov 9	Nov 10	Nov 12	Nov 13	Nov 21	Nov 22	Nov 27*	Dec 18
Hemoglobin (gm)	14.0				13.5		14.0	15.5
Erythrocytes† (millions)	4.62				4.54		4.58	5.2
Leukocytes	1350	1500	1100	950	1200	950	1350	1100
Neutrophils	58	68	66	60	62	66	59	
Filament cells	36	48	34	43	52	58	47	
Non-filament cells	22	20	32	17	10	8	12	
Lymphocytes	38	22	26	35	32	34	37	
Monocytes	4	9	2	3	4	0	3	
Eosinophiles	0	0	0	0	2	0	0	
Basophiles	0	1	2	2	0	0	2	
Normoblasts	3	6	2	5	12	0	6	
Platelets	200,000			140,000				
Reticulocytes	12%							
Sedimentation time Linzenmeier technic	95 min							
Fragility	40-35							
Bleeding time Duke's method	19 min			6 min				
Clotting time	6 min	8 min						
Icterus index					9.7			

* Venous blood was used

† Well marked anisocytosis, poikilocytosis and slight polychromatophilia of the erythrocytes were observed

TABLE II
Adrenalin Test

Injection Nov 8 1 cc 1/1000 Epinephrine HCl Intramuscularly

	Before Injection	30 Minutes After Injection	50 Minutes After Injection	90 Minutes After Injection
Total leukocytes	1200	1600	800	900
Neutrophils	50	38	45	51
Filament cells	24	30	25	24
Non-filament cells	26	8	20	27
Lymphocytes	30	40	40	31
Monocytes	20	22	13	18
Eosinophiles	0	0	1	0
Basophiles	0	0	1	0
Normoblasts/100	1	0	0	1
Parasites	0	0	0	0
Platelets	Abundant			Abundant

TABLE III
Study of Material from Sternal Marrow and Spleen Puncture

	Sternal Marrow		Spleen Puncture November 26
	November 9	November 25	
Neutrophiles	45 33	39	18
Filament cells	14 00	11	10
Non-filament cells	31 33	34	8
Lymphocytes	31 00	27	30
Monocytes	7 33	12	24
Eosinophiles	0	0	0
Basophiles	0	1	0
Myelocytes	16 33	7	0
Premyelocytes	0	4	1
Myeloblasts	1 00	4	4
Normoblasts	8 66	6	11
Endothelial leukocytes	0	0	12
Polychromatophilia	Moderate	Increased	Marked

and firmly adherent to the parietal pericardium around the base of the heart. There was no excess fluid, and the heart was not abnormal.

The spleen was greatly enlarged, measuring 29 by 18 by 9 cm and weighing 2700 gm (figure 2). Its lower pole was opposite the left iliac crest. Its outer surface was smooth, dark red in color and covered with fibrinous material. A large, firm, white area measuring 9 by 6 by 4 cm and grossly resembling a large infarct was situated at the upper pole. On section the surfaces were dark red, somewhat fibrous and showed no definite pattern. The white area was surrounded by numerous small areas of similar tissue measuring 2 mm in diameter and extending for some distance into the substance of the spleen. No abnormality was discovered in the splenic vein and artery. The lymphatic system was grossly normal except for large pearly-white lymph nodes at the porta of the liver.

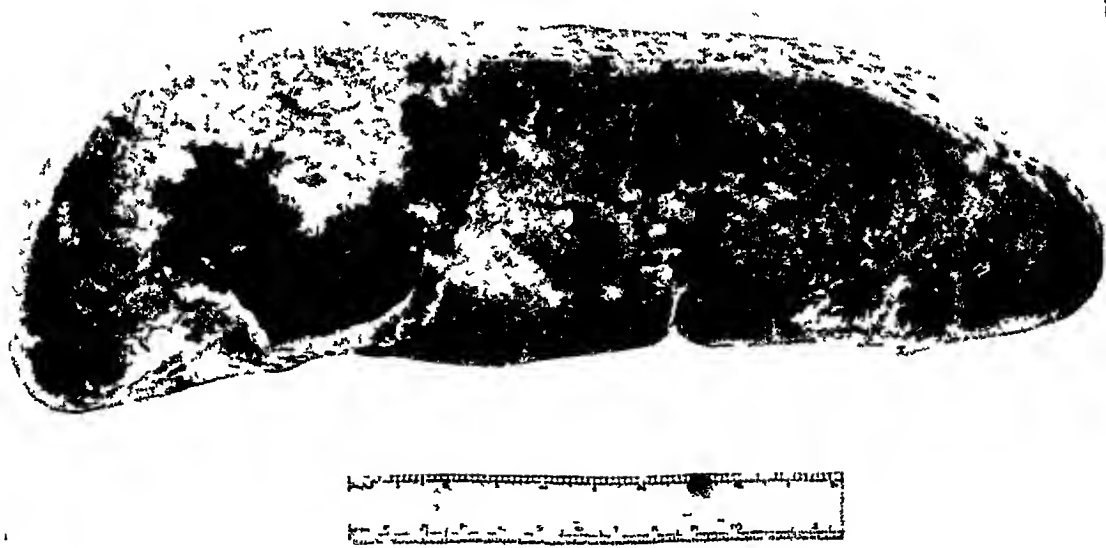


FIG 2 Gross section of spleen

The liver weighed 2050 gm. Its surface was covered with fibrinous exudate. On section the normal lobular markings were visible. In addition myriad pale gray nodules averaging 3 mm in diameter and appearing as focal necroses were noted. The portal vein and its tributaries were slightly dilated but not otherwise abnormal.

Microscopic Examination Spleen The capsule was thickened. The normal architecture was altered and the Malpighian follicles were small and indistinct. The reticulum appeared active. There were many agminations of brown pigment. The pulp sinuses were patulous and the pulp cords were filled with red blood cells. Some of the trabeculae were thickened. In some areas the splenocytes were filled with brown pigment. A large anemic infarct surrounded by an area of marked hyperemia was observed. There were small collections of polymorphonuclear cells as well as many small areas of tuberculous necrosis with giant cell formation. The section stained with carbolfuchsin demonstrated myriad acid-fast bacilli singly and in groups which were distributed throughout all portions of the section but in greatest numbers in the areas of necrosis (figures 3 and 4).

Liver The liver showed small areas of tubercle formation with necrosis. The regularity of the lobular structure was impaired. Some of the parenchymal cells contained two nuclei. The triangular spaces were distinct and in some of them was seen diffuse infiltration of uninucleate cells of the phagocyte series. There were a few polymorphonuclear cells adjacent to the triangular spaces. Small particles of brown pigment were present in the sinusoids. Giant cells were observed in some areas of necrosis (figure 5).

COMMENT

This case presents the chronic form of massive caseating tuberculosis of the spleen. The important clinical features were evidence of chronic infection with intermittent fever, occurrence of petechiae, extreme splenomegaly, moderate hepatomegaly and acites, and a gradual failing course which progressed to death nine months after onset of the recognized symptoms.

The blood showed no anemia or polycythemia (table 1), but normoblasts were constantly present. There was marked leukopenia with an absolute reduction in the total number of all white cells. Attempts to increase these failed. After intramuscular injection of 1 cc of epinephrine HCl, the total number of leukocytes increased from 1200 to 1600 per cubic millimeter in 30 minutes but then decreased to 800 per cubic millimeter in 50 minutes. The leukopoietic tissues were apparently unable to respond to this injection with the usual leukocytosis.⁵ Sternal bone marrow was obtained on two occasions by needle puncture (table 3). The specimens revealed a moderate increase in the immature myeloid elements and a slight diminution in the number of nucleated red blood cells.⁶ Material obtained from the spleen by puncture showed immature myeloid elements and normoblasts which suggested the presence of hematopoiesis in the spleen (table 3). Tuberculin tests were positive with bovine but negative with human old tuberculin. The ascitic fluid contained tubercle bacilli, these were not differentiated as to strain.

Autopsy revealed a spleen weighing 2700 gm, one of the largest tuberculous spleens on record.^{4, 7, 8, 9} Tubercle bacilli were demonstrated in the microscopic section of the spleen. One small caseous lymph node in the mediastinum and many small tubercles scattered throughout the liver were the only other areas of tuberculosis discovered.



FIG 3 Photomicrograph of spleen showing tuberculous necrosis and giant cell formation

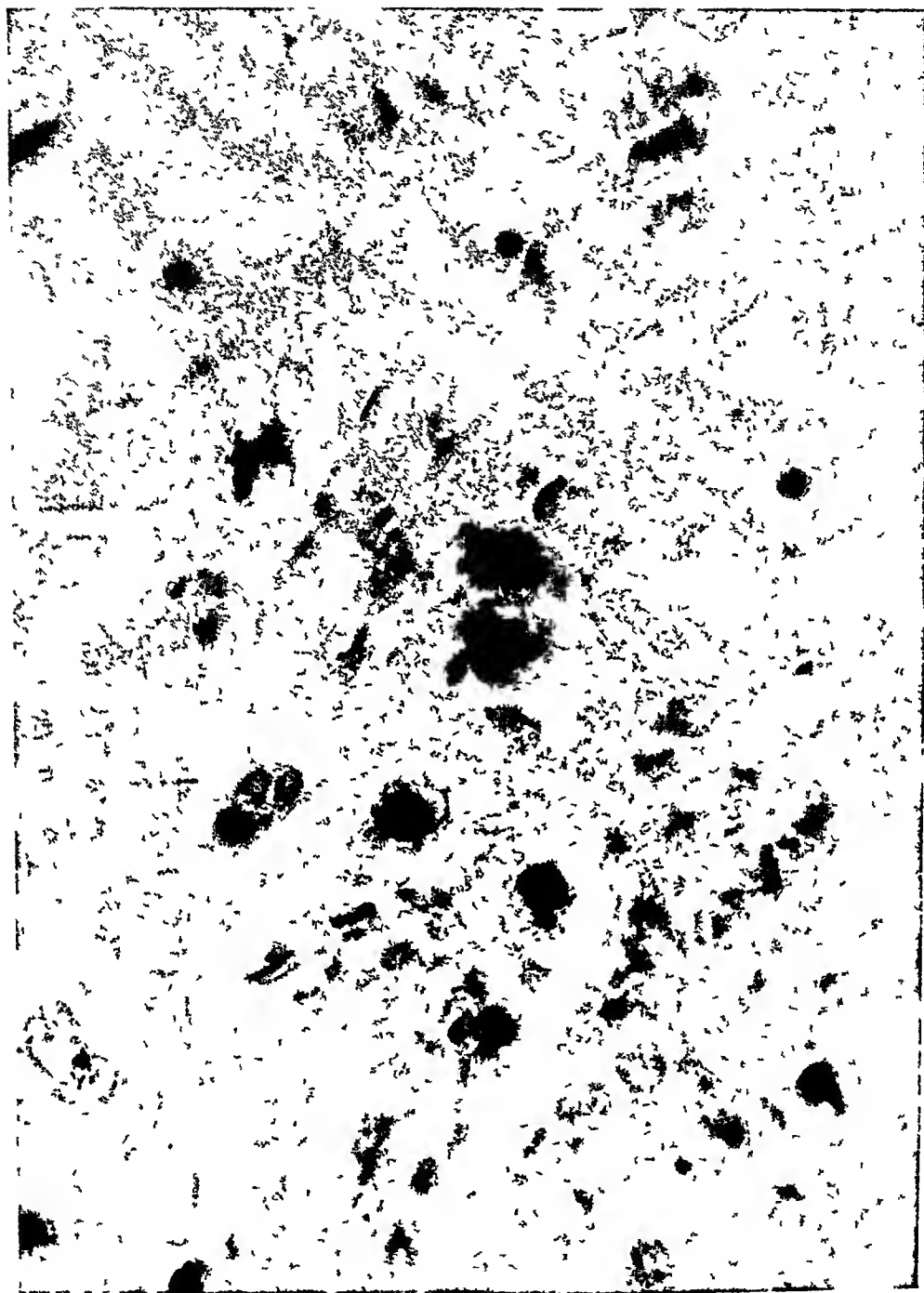


FIG 4 Photomicrograph of spleen showing tubercle bacilli

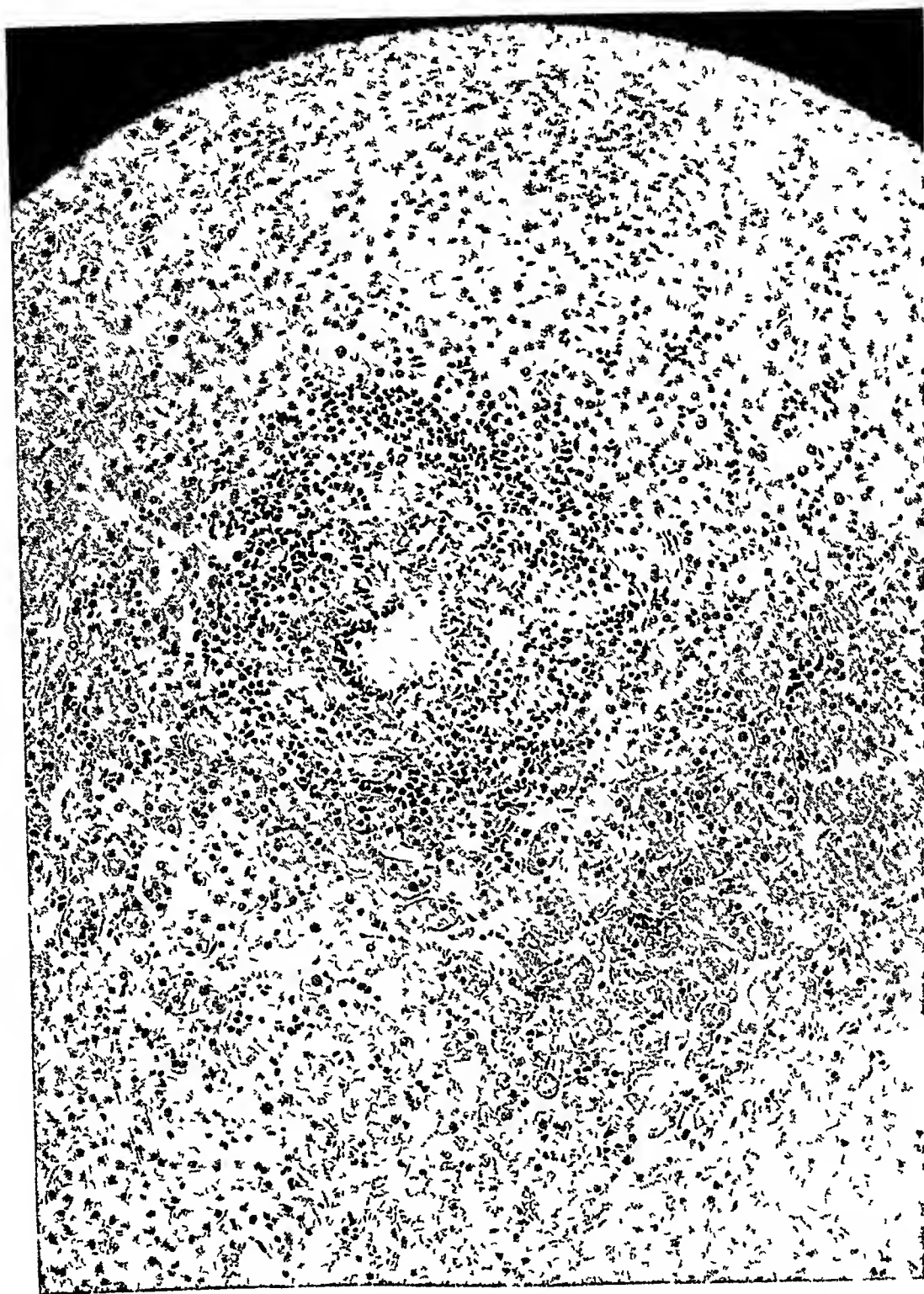


FIG 5 Photomicrograph of the liver showing an area of necrosis

DISCUSSION

In the course of tuberculosis of the spleen, abnormalities almost always occur in the blood and the blood forming organs. The mechanisms which operate to bring about these changes remain obscure. The subject has been discussed recently by Engelbreth-Holm.⁹ A study of the reported cases does not reveal any uniform blood picture. Anemia, polycythemia, leukopenia, leukocytosis, normal erythrocyte count and normal leukocyte count have all been observed in cases of tuberculous splenomegaly.^{1, 2, 3, 4, 7-21} Anemia with leukopenia or normal leukocyte count is most frequently observed. Hemorrhages from the gastrointestinal tract or purpura sometimes occur.^{4, 7, 8, 9}

Erythrocyte and hemoglobin values were normal in the case reported. However, the elevation of the icterus index, the increase in reticulocytes, the presence of normoblasts in the spleen and blood, the polychromatophilia and the variation in the size and shape of the red blood cells were suggestive of increased destruction of red blood cells. A profound leukopenia was associated with a slight increase in non-filament neutrophilic cells in the blood and an increase also in immature myeloid elements in the bone marrow. The presence of immature myeloid elements and normoblasts in the spleen suggested active hematopoiesis in this organ. These abnormalities in the hematopoietic tissues apparently resulted from extensive disease of the spleen.

SUMMARY

The clinical, laboratory and autopsy findings of a case of localized tuberculosis of the spleen are presented. The clinical characteristics were a gradually failing course with intermittent fever, petechiae, extreme splenomegaly, hepatomegaly and ascites. Autopsy revealed a very large tuberculous spleen in which tubercle bacilli were demonstrated. The only other areas of tuberculosis discovered were small patches of tuberculous necrosis in the liver, caseous nodes at the porta of the liver and one caseous paratracheal node. Extreme leukopenia persisted in spite of attempts to increase the number of circulating leukocytes. The immature myeloid elements in the sternal marrow were increased, and there was evidence of hematopoiesis in the spleen. Anemia did not occur.

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PSITTACOSIS; REPORT OF A FATAL CASE TREATED WITH SODIUM SULFAPYRIDINE*

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PRIOR to the epidemic of 1929-1930 psittacosis was almost unknown in this country except for a few sporadic cases. It has, however, been recognized as a disease, and the association with parrots noted, for at least 60 years. Its infrequency in recent times has tended to cause it to be almost forgotten. Many cases have undoubtedly gone unrecognized and were considered to be atypical typhoid, influenza, or influenzal pneumonia. It has seemed worthwhile, therefore, to present the following case and to call attention again to this disease.

CASE REPORT

S B, a woman aged 44, entered Sydenham Hospital, April 15, 1940, complaining of pain and swelling in the perianal region, associated with a purulent discharge and itching, of several months' duration. She had had no previous illnesses of importance.

Physical examination disclosed a well developed and well nourished woman, not appearing acutely ill. The pupils reacted to light and accommodation. There was no

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nasopharyngeal congestion. The lungs were clear. The heart showed no abnormal findings. The spleen was not felt. The extremities were normal. The reflexes were all active. Rectal examination showed the presence of a simple fistula in ano at the posterior commissure. The rectal temperature was 100.4°F , the pulse 88 and the respirations 22.

On April 16 the fistula was excised under general anesthesia.

On April 19 the patient complained of pain in the neck and in the joints. The temperature rose to 102°F . The operative wound looked clear and appeared to be healing satisfactorily. The lungs remained clear. Nothing definite could be found to account for the fever, which continued to mount, with remissions, until it reached 104.6°F on April 24 (figure 1). Additional history obtained at this time revealed

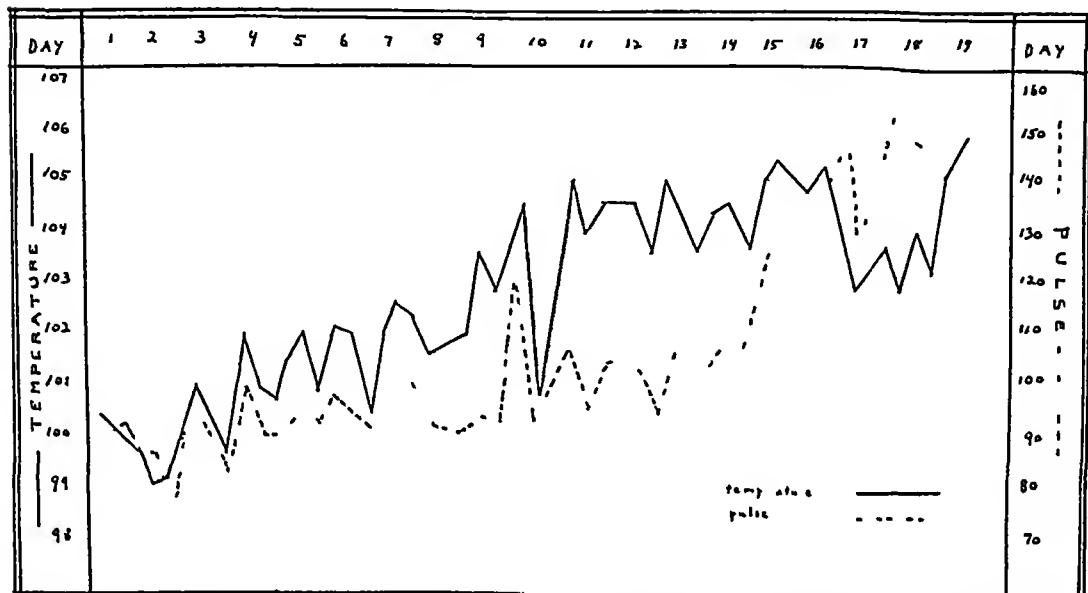


FIG 1 Temperature and pulse. The pulse is relatively slow in relation to the temperature, except in the terminal phase.

that on April 10 the patient had been bitten on her right index finger by an African love bird recently imported from California and that the bird had died two days later.

On April 26 the patient appeared toxic and markedly apathetic. The temperature was 104.6°F , the pulse 100, and the respirations 24. Except for some paravertebral dullness the lungs appeared clear. The heart showed a relative bradycardia (figure 1) but no murmurs. The spleen was not felt. The joints were normal. There was no adenopathy. The neurological examination was entirely negative. The history of exposure to the love bird suggested the diagnosis of psittacosis. Chemotherapy was begun on this date. The patient received intravenously 10 grams of sodium sulfapyridine in four divided doses. The subsequent daily intravenous dose of this drug was 8 grams.

The urine was essentially negative, except for a very faint trace of albumin. The red blood count was 3,750,000, with 67 per cent hemoglobin. The white blood count was 11,300 with 77 per cent neutrophils of which 12 were band forms and 65 segmented, 18 per cent lymphocytes, and 5 per cent monocytes. The smear showed no malarial plasmodia. Both aerobic and anaerobic blood cultures were sterile. Agglutination tests for typhoid, paratyphoid, undulant and typhus fevers were all negative.

A roentgenogram of the lungs taken April 25 (figure 2) showed a bilateral pneumonic process, spreading from the hilar region on the right and involving the lower lobe on the left side

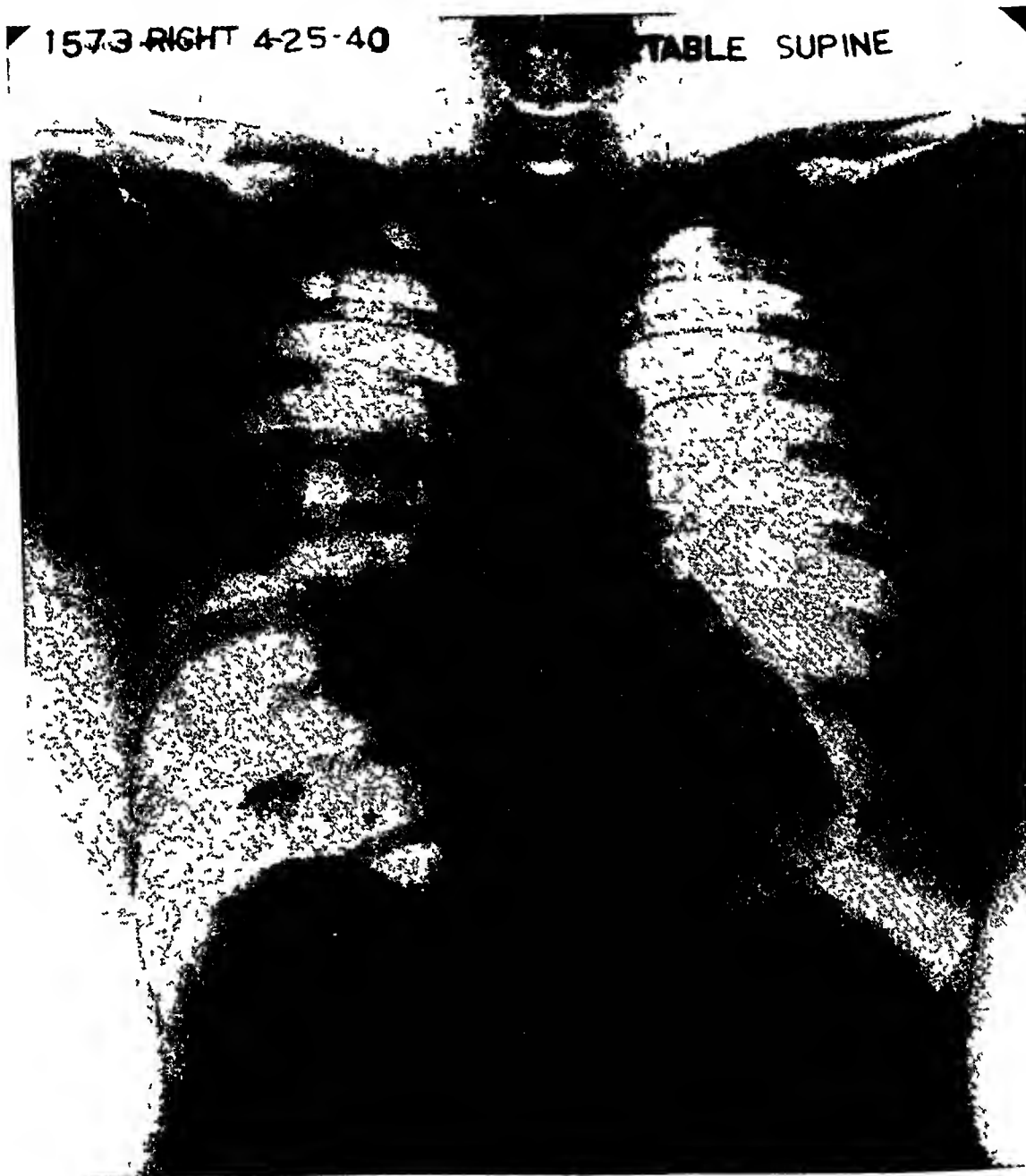


FIG 2 Appearance of lungs. Note right hilar involvement with spread into the adjacent parenchyma. There is also involvement of the lower left lung field.

A specimen of the patient's blood was submitted to Dr Karl F Meyer, of San Francisco, who reported that the serum gave a strong complement fixation reaction with psittacosis antigen in a dilution of 1 to 128. This established the diagnosis of psittacosis.

The patient's condition became progressively worse. The temperature reached 105.6° F on April 30. She was in a semistupor and markedly dyspneic. Cyanosis

was moderate. There were numerous moist and subcrepitant râles over both lungs. The daily administration of sodium sulfapyridine intravenously was being continued.

The roentgenogram of April 30 (figure 3) showed further extension of the pneumonic process, involving the greater part of the right lung.



FIG 3 Five days later further extension of process on right to involve almost the entire lung field

The blood count showed now 3 150 000 red blood cells, with 58 per cent hemoglobin, and 9950 white blood cells with 77 per cent polymorphonuclears, of which 17 were band and 60 segmented forms, 8 per cent monocytes, and 15 per cent lymphocytes. The sputum did not show the presence of pneumococci. The blood sulfapyridine level

was 10.3 mg per cent. The urine showed now 4 plus albumin, 2 plus urobilinogen, a few granular casts, 15 to 20 red blood cells and 6 to 8 white blood cells per high power field.

On May 3 the patient's general condition was very grave. The temperature was 105.8° F, the pulse 170, and the respirations 48. She died the same day.

Autopsy (May 4, 1940, Dr. A. M. Ginzler, 16 hours after death). The body was that of a fairly well developed and well nourished 44 year old white female. The abdomen was moderately distended. There was slight cyanosis of the lips and nail beds. Otherwise, the body presented no noteworthy features externally. The peritoneal cavity contained no free fluid. The peritoneal surfaces were smooth and glistening. The loops of small bowel were slightly distended. The liver margin was 1½ fingers'-breadth below the right costal margin. The spleen was not visible. The abdominal viscera were otherwise normal in appearance. The domes of the diaphragm were at the level of the fourth interspace on either side. The pleural spaces contained no fluid and were free of adhesions. The pleural surfaces were smooth and glistening. The right lung weighed approximately 1125 grams. The right lower lobe was large, heavy and firm throughout except for small areas of subcrepitant consistency at the periphery. On section the cut surfaces were reddish-gray to reddish-brown and, for the most part, dry and granular, obscuring the normal alveolar markings. At the periphery there were areas somewhat moist and congested, and moderately air-containing. The upper and middle lobes contained irregular areas of granular consolidation toward the hilus, and in the remainder showed considerable edema and congestion. The left lung weighed approximately 725 grams. The lower lobe showed almost complete consolidation. The upper lobe was fairly dry and moderately emphysematous. The trachea and bronchi showed considerable mucosal congestion and contained a small amount of frothy fluid. The tracheo-bronchial lymph nodes were moderately swollen. The pulmonary vessels appeared grossly normal. The heart was essentially normal in size and appearance. The pericardial surfaces were smooth and glistening. The chambers and valves appeared grossly normal. The myocardium was moist and reddish-brown, there was no gross evidence of fibrosis. The coronary vessels and aorta were thin, elastic, and of normal caliber. The liver weighed approximately 1300 grams. The capsule was thin and smooth. On section the cut surfaces were uniformly yellowish-tan. The lobular markings were not prominent. The hepatic and portal vessels, gall-bladder and biliary tract showed no gross changes. The spleen weighed 150 grams and was moderately soft in consistency. The capsule showed no thickening. On section the pulp was markedly congested. The follicles were distinct. The gastrointestinal tract showed irregular areas of mucosal congestion throughout. The pancreas showed no gross changes. The adrenals appeared normal. The kidneys weighed approximately 300 grams together. The capsules stripped easily, exposing smooth grayish-brown surfaces. On section the cortices appeared slightly swollen. The cortical and medullary markings were distinct and regular. The pelves, renal vessels, ureters and bladder showed no gross pathological changes. The uterus was moderately enlarged due to several intramural and subserous fibroid nodules. In addition to the tracheobronchial nodes, there was also moderate enlargement of the mediastinal and para-aortic nodes.

Microscopic Examination. The lungs showed extensive pneumonic consolidation (figure 3). The exudate was markedly fibrinous in character and only moderately cellular. The cells consisted chiefly of large macrophages with considerable granular cytoplasm (figure 4). Many contained round, basophilic, intracytoplasmic inclusions. Scattered neutrophils were present in small numbers. The interalveolar septae were moderately thickened owing to capillary congestion and mononuclear infiltration. Occasionally they were lined by endothelial-like cells with plump nuclei. The pleura remained essentially normal even where overlying pneumonic parenchyma. Other

portions of the lung showed edema and congestion. The bronchi contained a moderately cellular, mucoid exudate, but showed only mild or no inflammatory reaction of their walls. The lymph nodes showed a moderate inflammatory hyperplasia. Many of the sinusoids were crowded with large macrophages of the type seen in the pulmonary alveoli (figure 5). One section showed a small area of necrosis. There were degenerative changes of the liver cells, particularly about the central veins, and a diffuse moderate fat vacuolization. The liver capillaries were dilated. The splenic pulp was markedly congested and showed moderately increased cellularity due to the



FIG 4 Section of the lungs under low power ($\times 100$) showing consolidation

presence of polymorphonuclear, plasma and mononuclear cells. Sections of the remaining organs showed no noteworthy histopathologic features.

Gross Anatomic and Microscopic Diagnoses Bilateral confluent lobular pneumonia, inflammatory hyperplasia of lymph nodes, fatty degeneration of liver, fibromyomata of uterus.

COMMENT

This case illustrates many of the typical features of psittacosis. The history of exposure to the recently acquired love bird was an important lead in making the correct diagnosis. Indeed, it would be too much to expect that the nature of the infection would be recognized without knowledge of a possible source of exposure. In this connection it is to be noted that all or nearly all birds belonging to the family Psittacidae are actual or potential carriers of the disease. The shell parakeet is regarded as the most important vector of the illness, for the reason that this bird enters into commerce in large numbers.

The investigations of Bedson,¹ Krumwiede,² and Rivers,³ and their respective co-workers, furnish ample evidence that a filterable virus is the etiologic agent of this disease.

The incubation period has been estimated to range from seven to 14 days, although it may occasionally be prolonged to more than a month. In our case it was short, probably eight days.

Except for the pulmonary involvement, our case showed a marked resemblance to typhoid fever. This is a common observation. The patient frequently presents a typhoid-like state, with headache, disorientation and marked droopiness progressing to stupor. Rose spots may occur about the end of the first

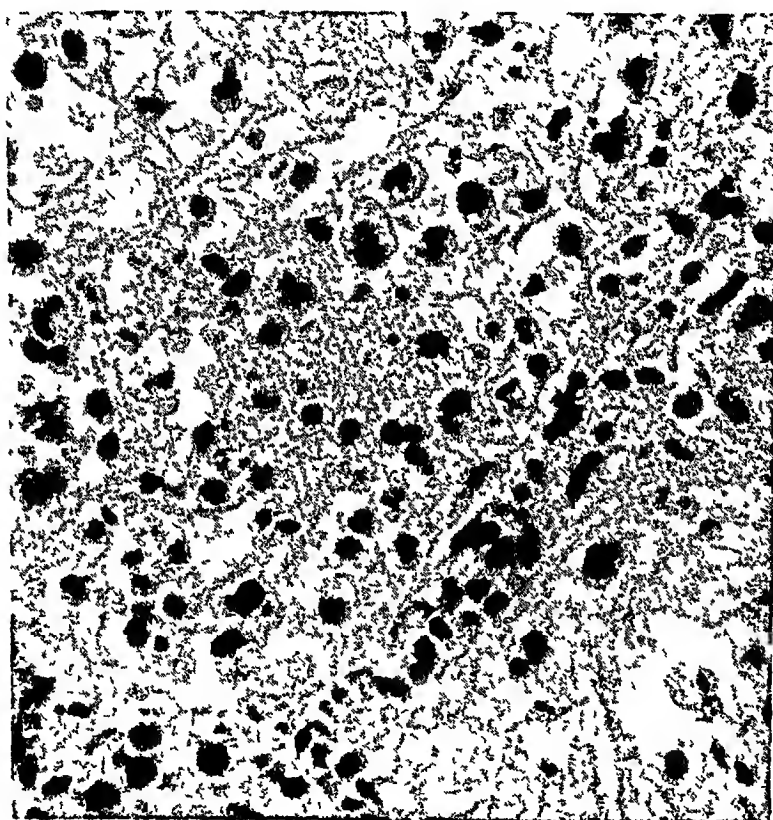


FIG 5 Section of the lungs under high power ($\times 500$) showing the fibrinous and moderate cellular exudate. The cells are predominantly large mononuclear phagocytes.

week. The spleen, however, is as a rule not palpable. The fever when recorded is usually 100° to 102° F, and tends to rise to a height of 103° to 105° F with irregular remissions during the second week. The pulse is likely to be slow in relation to the temperature. This pattern was observed in our case, except in the terminal phase (figure 1), when the pulse became very rapid and feeble.

As a rule, pneumonia develops early and is the most striking feature of the disease. There is usually but little cough or expectoration early, but these develop later. The cough is usually non-productive. Dyspnea and cyanosis are present only when there is extensive pulmonary involvement. Early in the disease there may be very meager or no physical signs in the lungs, although the roentgen

gram may show at the time a definite pneumonic process. This was observed in our case (figure 2). As the consolidation spreads to involve a lobe or more, râles and other signs become apparent. It should be noted that in spite of fairly marked pulmonary involvement on April 26, our patient presented no symptoms referable to the chest. There was no increase in rate of respiration, no pain on breathing, no cough and no expectoration.

As shown by our case, the white blood count is usually normal or slightly above normal, but a leukopenia is not infrequent. Our patient had also a moderate anemia. Albuminuria is a very constant accompaniment after the disease is established. This was demonstrated in our case.

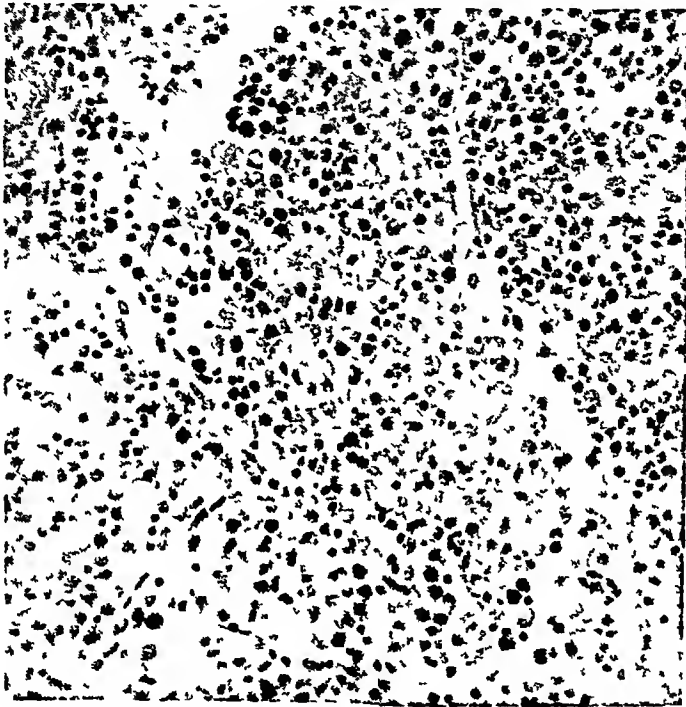


FIG 6 Medium power ($\times 250$) section of lymph node showing sinusoid crowded with large mononuclear phagocytes

Bedson⁴ was the first to point out that the patient's serum will fix complement in the presence of a psittacosis antigen, and he stressed the value of this reaction as a diagnostic procedure. Rivers⁵ and his co-workers demonstrated that the diagnosis can be confirmed also by inoculation of the patient's sputum into white mice. The complement fixation test in our case was strongly positive.

The case fatality rate is generally given as 20 per cent. Extensive pulmonary involvement is regarded as an ominous prognostic factor. Several observers have noted that children and young adults tend to have mild attacks and that deaths are rare in patients under 30 years of age.

Treatment has in the main been symptomatic. Blood transfusions and administration of liver extracts have been recommended. Convalescent serum has been tried by several investigators and found to be of very doubtful value. So

far as we know, this is the first record in this country of the use of sulfapyridine or its sodium salt in the treatment of psittacosis

The pathologic findings presented by this case of psittacosis were quite typical. The lungs showed the characteristic inflammatory process which is primarily focal or lobular and apparently not closely related to the bronchioles. The alveolar exudate was markedly fibrinous in character and only moderately cellular (figures 4 and 5). The cells were chiefly large mononuclear macrophages with considerable granular cytoplasm. Scattered neutrophils were present in small numbers. The pleura, as has been frequently observed, was essentially normal. The lymph glands (figure 6) and to a lesser degree the spleen also showed the presence of large macrophages of the type seen in the pulmonary alveoli. The liver showed areas of degeneration, particularly about the central veins. There were no other remarkable changes.

The authors wish to express their gratitude to Dr Karl F Meyer, of San Francisco, for his prompt and valuable assistance in establishing the diagnosis, and to Dr Dana W Atchley, of the College of Physicians and Surgeons, Columbia University, for valuable suggestions and criticisms.

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TRICUSPID STENOSIS. REPORT OF A CASE WITH INVOLVEMENT OF ALL FOUR VALVES OF THE HEART *

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TRICUSPID stenosis is an uncommon valvular lesion of the heart and one rarely diagnosed clinically. Leudet¹ in 1888, J B Herrick² in 1897, W W Herrick³ in 1908, Fitcher⁴ in 1911, and Zeisler⁵ in 1933 have collected cases. Zeisler could find but 250 autopsied cases in the world literature and of these only 12 per cent were correctly diagnosed before death. Formerly there was discussion as to whether the lesion of tricuspid stenosis is congenital or acquired. For many years the great majority of cases have been considered as due to rheumatic heart disease. About 50 per cent give a history of rheumatic fever. Females are three times more frequently affected than males. The greatest number of those affected die between the ages of 20 and 30. Tricuspid stenosis is rarely present alone. It is usually accompanied by lesions of one or more of

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the other valves. The mitral is most commonly affected so that in the majority of cases tricuspid stenosis and mitral stenosis coexist.

The important clinical signs of tricuspid stenosis are produced mechanically by a diseased valve obstructing the flow of venous blood between right atrium and right ventricle.⁶ In an attempt to overcome this obstruction the atrium hypertrophies. Partially failing to overcome it the auricle dilates. This dilatation of the vena caval openings into the auricle with the consequent loss of the valvular action of the musculature surrounding them. Then the cavae dilate to accommodate the backflow. The result of this mechanism is that the blood in auricle, venae cavae, jugulars and liver is under greatly increased pressure. Lacking the protection against backflow afforded by interposed valves it pulsates strongly in response to right auricular systole. It also pulsates in response to right ventricular systole. Since tricuspid insufficiency always accompanies tricuspid stenosis, a portion of the right ventricle's blood will be forced into the right auricle, thereby starting a pulse that travels to jugular and liver.

Clinical Findings (1) Dyspnea on exertion.⁷ (2) Cyanosis. (3) Unilateral enlargement of heart. (4) Elevated venous blood pressure. (5) Attention and presystolic pulsation of cervical veins with large "A" wave in phlebogram due to strong right auricular systole. (6) Enlargement of liver with double pulsation of liver, detectable by observation, palpation or hepatojugular reflex. One pulsation is synchronous with the "A" wave of jugular pulse and it is produced by a strong right auricular systole. The other is synchronous with the "V" wave of jugular pulse and like it is produced by right ventricular systole. (7) Disappearance of "A" waves in phlebogram and hepatojugular reflex (the double liver pulsation either giving way to a single pulsation or disappearing altogether) upon the failure of the right auricle or onset of auricular fibrillation or nodal rhythm.⁸ The single wave or "V" wave of phlebogram and hepatogram is due to tricuspid insufficiency and was called the ventricular form of the venous pulse by Mackenzie.⁹ (8) Concomitant mitral stenosis which produces a rough diastolic or presystolic murmur at the apex. The murmur of tricuspid stenosis, also a diastolic murmur, is usually heard at the xiphoid process and may or may not be differentiated from that at the apex. The presence of systolic murmurs at apex and xiphoid may complicate differentiation. (9) Ascites out of proportion to the peripheral edema due to the congestion of the lungs. (10) Cirrhosis of the liver¹⁰ following prolonged chronic passive congestion. Either may give rise to jaundice.¹¹

Differential Diagnosis Chronic constrictive pericarditis and pericardial effusion must be differentiated from tricuspid stenosis. By obstructing venous return to the right auricle they may give rise to high venous pressure, hepatic megaly and ascites. The differentiation should not be difficult because of the normal-sized, quiet and fixed heart of constrictive pericarditis and the dilated, shaped heart with weak sounds and paradoxical pulse of pericardial effusion. However, it is worthy of note that an auricular liver pulse has been reported in both these conditions.^{12, 13}

To differentiate tricuspid stenosis from tricuspid insufficiency may be difficult, particularly in the end stages of heart disease. Tricuspid insufficiency will, as long as the right ventricle is strong enough and in spite of the presence of cardiac arrhythmia, give a liver pulse consisting of one big wave in contrast to the two waves of tricuspid stenosis. However, this differentiation holds

only so long as the patient with tricuspid stenosis has a normal cardiac rhythm. If auricular fibrillation should supervene, the "A" wave of auricular systole, so diagnostic of tricuspid stenosis, would disappear leaving the single "V" wave of tricuspid insufficiency.

Tricuspid stenosis cannot be diagnosed in a case of mitral stenosis before the characteristic double pulsation of the liver appears. It may be suspected in a young girl¹⁴ from the presence of a diastolic murmur at the xiphoid which has different characteristics from the mitral murmur.

Probably the chief reason for the rarity of the diagnosis of tricuspid stenosis is a concomitant cardiac arrhythmia which deprives the right auricle of its ability to contract in systole and give rise to the large "A" wave in the liver pulse.

CASE REPORT

D F, a 19-year-old unmarried colored girl, was first seen by us on her second admission to Emergency Hospital in May 1938 complaining of swelling of the face, abdomen and legs, shortness of breath, and a cough sometimes productive of bloody sputum. She had been suffering from heart trouble for 21 months and had had several hospital admissions during this time. At the beginning of her illness the important findings had been puffiness of the face, slight ankle edema, coarse râles at the lung bases, an enlarged heart with signs of mitral stenosis, an enlarged liver, a venous blood pressure of 110 mm of saline and a four plus Kahn reaction. After several months signs of aortic insufficiency had been detected. About nine months before we saw her the presence of a to-and-fro murmur at the tricuspid valve area, a pulsating liver and an elevated venous pressure (235 mm saline) had led to the diagnosis of tricuspid insufficiency. About a month before we saw her she had pneumonia involving the right lower lung. There was no past history of rheumatic fever, but she had had frequent sore throats. One and one-half years before the onset of heart trouble she had been hospitalized for an acute tonsillitis and at this time heart disease had not been discovered.

The patient lay flat in bed and did not appear acutely ill. There was a visible jugular pulsation. The heart was enlarged to the right and left, with the point of maximum impulse in the fifth interspace nearly in anterior axillary line. Measurements were 13.5 cm to the left in the fifth interspace and 7 cm to the right in the fourth interspace. Figure 1 is a roentgenogram of the heart. There was an intense presystolic thrill at the apex. There was a to-and-fro murmur over the entire precordium. At the apex the loudest murmur was a rough, low-pitched, presystolic murmur ending in a blurred first sound. The second sound was obliterated by another softer murmur running through diastole and joining the rumbling presystolic. The beginning and ending of a systolic murmur could not be made out owing to the prominence of the diastolic. Over the lower sternum and upper portion of the liver the rumble gave way to a musical to-and-fro murmur with the diastolic phase of longer duration than the systolic. At the base of the heart A_2 and P_2 were not heard. Here the to-and-fro murmur was faint but the diastolic phase was heard along the left sternal margin and sounded like that of aortic insufficiency. There was no Corrigan pulse. There was a visible and palpable liver pulsation apparently synchronous with the jugular pulsation. The liver was three fingers' breadth below the costal margin. The heart rate and rhythm were normal, and the lung bases were clear. There was no edema of the extremities, and no ascites.

Venous blood pressure was 345 mm saline.

Electrocardiographic findings were: Increased P-R interval, 0.23 second. Right axis deviation. A high, broad and split P-wave in Leads I and II. T-wave inverted in Lead III.

Polygraphic tracings were taken of the jugular vein, liver, carotid artery and apex beat of the heart (figure 2) The liver tracing showed two distinct waves, one due to auricular systole and one to ventricular systole The A-C interval of the jugular pulsation, like the P-R interval of the electrocardiogram, was prolonged Simultaneous stethographic and electrocardiographic tracings were obtained which showed the characteristics of the various heart murmurs and a P-R interval of 0.28 second (figure 3)



FIG 1 Fluorogram of the heart

Several observers later noted that the systolic murmur at the base of the heart was transmitted into the neck vessels, which suggested the presence of aortic stenosis Complete diagnosis at this time was chronic cardiac valvular disease (rheumatic) mitral stenosis and insufficiency, aortic stenosis and insufficiency, and tricuspid stenosis and insufficiency

During the following nine months from June 1938 until her death in March 1939 the patient was bedridden either at home or in the hospital The heart became tre-

mendous, filling most of the anterior thorax. There was one episode of fever and hemoptysis with consolidation of the right lower lung. There was another stormier episode of tachycardia accompanied by premature contractions. The venous pressure went as high as 400 mm of saline. The liver remained enlarged and pulsating, and the last few months were characterized by sacral edema and a marked ascites requiring diuretics and paracenteses.

Temperature, pulse and respiration were within normal limits generally except for the episodes of tachycardia and hemoptysis. The blood pressure was 125 mm Hg systolic and 70 mm diastolic. Blood counts were not remarkable. The blood Wassermann reaction was four plus and for this reason she received bismuth. Sedimentation rates were within normal limits. Basal metabolism on two occasions was plus 20 per cent and plus 8 per cent. Blood non-protein nitrogen was 28 to 41 mg per 100 c.c. Kidney function test gave a reading of 72 per cent in two hours. The urine was normal until the last few weeks of life when it showed albumin, casts and red blood cells.

Autopsy There was some cyanosis of nail beds. The abdomen was distended with fluid, and there was slight edema of the lower extremities.

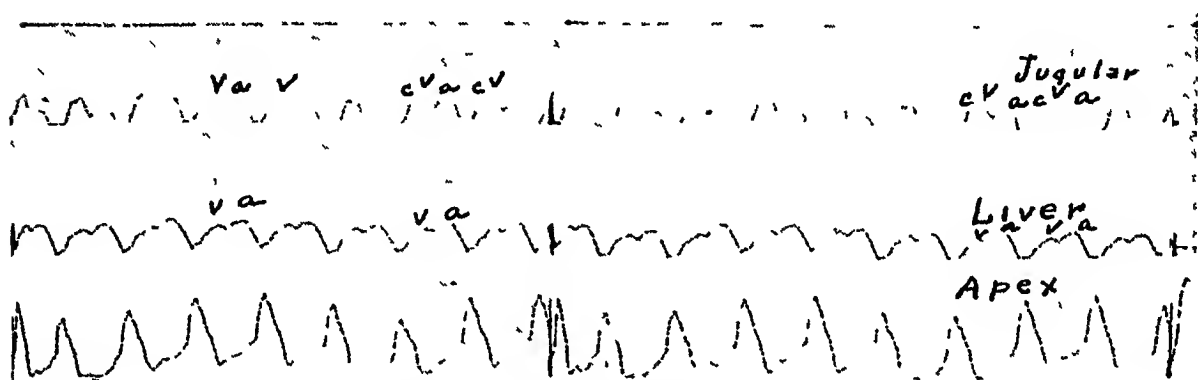


FIG 2 Polygraphic tracing of jugular vein, liver and apex beat

The heart was tremendously enlarged, almost filling the anterior thorax. The pericardial sac contained 200 c.c. of clear yellow fluid. The heart weighed 590 grams, the right side being about three times the size of the left. The right atrium was especially large, its musculature tremendously hypertrophied and its endocardium thickened. There was a stenotic lesion of the tricuspid valve which had glued together the three cusps so that they formed a fibrous membrane, the opening of which scarcely admitted the tips of two fingers (figure 4). The right ventricle was not much hypertrophied, measuring 7 mm in thickness. The free edges of the cusps of the pulmonic valve were involved in a fibrous tissue which thickened them into a rolled edge 1.5 cm in thickness. A few small intramural thrombi were found in the left auricular appendage. The endocardium of the left atrium was quite thickened. The mitral valve was markedly stenotic with a fish mouth opening which barely admitted the tip of the little finger. The left ventricle was normal. There was a rather marked fibrosis with thickening of all four edges of the aortic valve. There was also some glueing together of the aortic cusps at their bases. The coronary arteries and aorta were normal. The superior and inferior venae cavae were tremendously dilated, the former measuring 4 cm across and the latter 6 cm.

There was no fluid in the pleural cavities, and there were no adhesions between lungs and pleura. The lungs were gray, subcrepitant, firm, and rubbery in consistency. On sections, they seemed quite dry, and there was no consolidation present.

The abdomen contained about one and one-half liters of clear fluid

The liver extended 3 cm below the rib margin. It was heavy, firm and nodular. It was estimated to be one and one-half times the normal weight, although it was not much over normal in size. It showed a variety of colors ranging from orange to red to deep purple. On section it cut with increased resistance. The cut surfaces showed the same variety of colors and numerous radiating scars of fibrous tissue. The venous

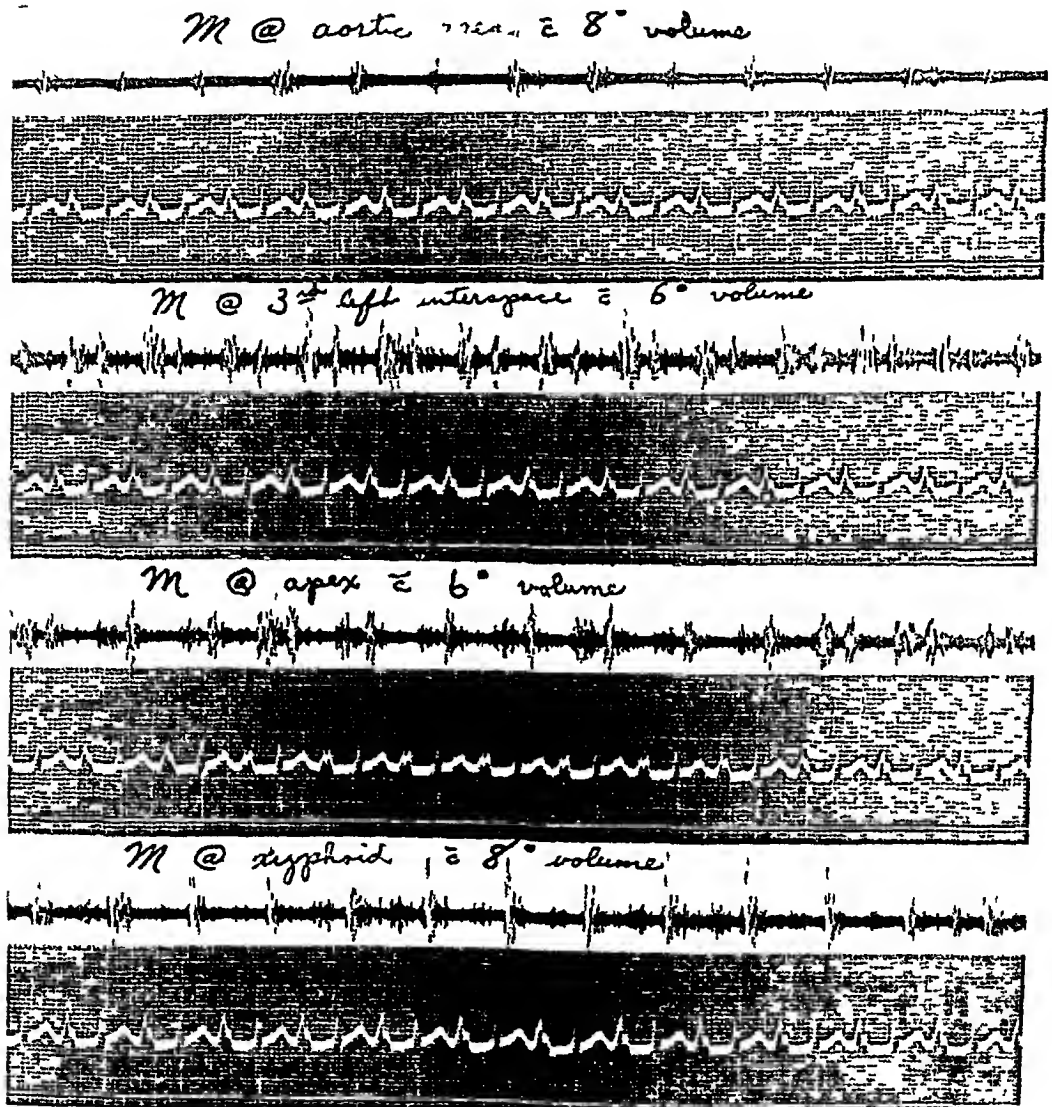


FIG 3 Simultaneous stethographic and electrocardiographic tracing

channels were much dilated and very pronounced. There was a lobulated appearance of the tissue and the finger was unable to dent the tissue with ease.

Microscopically there was one area suggesting an Aschoff body in the myocardium. The lungs showed a peculiar interstitial fibrosis recently described as a manifestation of rheumatic fever by Gouley.¹⁵ The liver was in great part destroyed by an intense fibrosis causing an atypical cirrhosis.

DISCUSSION

The progression of the valvular lesions in this patient, as indicated by the change in physical findings during the first year of cardiac symptoms, is interesting, from mitral to aortic to tricuspid. Pulmonic involvement was not diagnosed until postmortem examination. The patient lived for only one and one-



FIG 4 Photograph of the heart showing tricuspid orifice

half years after the discovery of tricuspid disease and only two and one-half years after the onset of cardiac symptoms. This is not in accord with the report of Thompson and Levine¹¹. They found that patients with tricuspid stenosis, although they get their symptoms at an earlier age, live longer after the onset of symptoms than those who have only aortic and mitral valve involvement. In

their series of 21 autopsied cases of tricuspid stenosis the average duration of symptoms was seven and one-half years

A very unusual feature in this case is the involvement of all four valves of the heart

To repeat what has been previously noted by numerous writers, tricuspid stenosis, by decreasing the volume of blood pumped into the pulmonic circulation, relieves the strain on the left auricle and thereby mitigates the signs of concomitant mitral stenosis such as dyspnea, accentuated pulmonic second sound, and congestion of the lung bases

Ascites out of proportion to edema of the lower extremities is characteristic of constrictive pericarditis as well as tricuspid stenosis. Apparently, the portal circulation is more vulnerable to elevated venous pressure than the vena caval. The reason for this is not clear. In the later stages of both diseases a cirrhosis of the liver consequent upon chronic passive congestion better explains this phenomenon. Chronic passive congestion of the liver accounts for the jaundice which combined with cyanosis may give persons with tricuspid disease a peculiar yellow-blue color

SUMMARY

Tricuspid stenosis has been discussed mainly from the diagnostic point of view and a case with autopsy reported illustrating the important signs of this disease. Incidentally, all four valves of the heart were affected by the rheumatic process

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CHOREA COMPLICATING POLYCYTHEMIA VERA; REPORT OF A CASE¹

By LAWRENCE M KOTNER, M D, *St Louis, Missouri*,
and

JOHN H TRITT, M D, *Fort William, Ontario*

ERYTHREMIA, or polycythemia vera, is a disease characterized by an increase in the erythrocyte count and volume of the circulating blood, splenomegaly, and various circulatory phenomena due to the increased viscosity of the blood. Neurological symptoms and signs are common in this condition as was emphasized by Vacquez and a little later by Osler in their original reports of this disease. Christian¹ emphasized the neurological manifestations of this condition and stated that the failure to keep these symptoms in mind leads to mistakes in diagnosis. In his report of 10 cases of polycythemia vera, headaches and vertigo were the most common presenting complaints. Blurring of vision, scotomata (often scintillating), hemianopsia, diplopia, paresthesia, paresis, paralysis, and speech disturbance were other central nervous system manifestations. He believed that in the earlier stages, the nervous symptoms resulted from simple circulatory disturbances secondary to the increased viscosity of the blood. In the late stages, he contended that cerebral softening or cerebral hemorrhage and local vascular lesions such as thrombosis were often to be found. Brockbank,² in an analysis of 56 cases at the Mayo Clinic, pointed out that headache predominated in 33 of these patients, vertigo in 30, general weakness in 15, fullness in the head, paresthesia and mental impairment in 11. Sloan³ reported the case of a man aged 40, with erythremia, who developed a thrombosis of the Sylvian artery, followed by a subarachnoid hemorrhage. This patient recovered. In another patient reported in his series the presenting complaint was a pruritus of seven years' duration. Adams⁴ found in nine cases of erythremia, six patients who presented themselves because of either headache, vertigo or paresthesia.

Chorea, however, as a complication of erythremia is rare. Umney,⁵ in 1909, was the first to report such an occurrence. His patient, a 34 year old female, had a red cell count of 9.5 million, and was known to have had erythremia for some eight years. She developed a speech disturbance which rapidly developed into a chorea, followed shortly by thrombosis of the left jugular vein. The

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chorea rapidly cleared but reappeared after one month, this time followed by edema of the lower half of the body, cough, dyspnea, anuria and finally death. The author thought that the chorea was on the basis of cerebral thrombosis. No autopsy was obtained. Pollack⁶ referred to a case, reported by Berdachzi in 1909, of a 50 year old woman who developed chorea from which she finally recovered after seven months. Her red cell count at the onset of the chorea was 109 million, and after recovery was 93 million. Pollack in 1922 reported the third case of chorea complicating this disease. The patient was a 38 year old woman who had complained of headache, vertigo, dyspnea, cyanosis, and blurring of vision for six months. Her red cell count was 81 million, the leukocyte count 8,500. This patient developed chorea which involved mainly the upper half of her body, and which lasted two months. Improvement was noted 10 days after roentgen-ray therapy to the long bones was started. This patient also recovered. Pollack believed that the underlying pathology here was either cerebral thrombosis or hemorrhage. In 1922 Doll and Rothschild⁷ in Germany cited six brothers and sisters, five of whom had Huntington's chorea. The youngest sister, who did not have chorea, was found to have a red cell count of 6,000,000, and a hemoglobin of 95 per cent. One brother with chorea had a red cell count of 65 million, a hemoglobin of 115 per cent, and a firm palpable spleen. Obviously, however, the etiology of the chorea here was entirely different from the first three cases reported above. In the French literature in 1933, Schiff and Simon⁸ reported the incidence of chorea in a 78 year old woman known to have had erythremia for at least five years. The chorea developed rather suddenly and was extremely violent. This patient had a red cell count of 68 million with a hemoglobin of only 90 per cent. The leukocyte count was 16,000. A lumbar puncture revealed xanthochromic fluid containing many red blood cells and 35 white blood cells per cu mm. The Pandy test was strongly positive. These authors, too, explained the disturbance on a vascular basis, probably thrombi and hemorrhages in the region of the basal ganglia.

In this paper we wish to present another case of chorea complicating erythremia together with the laboratory data and the autopsy findings.

CASE REPORT

This patient was first seen in 1935 when she was admitted to the hospital suspected of having a fractured pelvis. In the previous 15 years there had been five fractures of the bones of the lower extremities. Examination was essentially negative save for a dusky skin, markedly reddened mucous membranes and a palpable spleen. The red cell count was 94 million, white cell count 12,700, and hemoglobin 130 per cent. The bleeding time was 35 minutes, clotting time 2 minutes, clot retraction nil, blood sugar 94 mg per cent, non-protein nitrogen 29 mg per cent, blood diastase 20 (normal 80 to 150),⁹ blood calcium 11 mg per cent and glycolysis rate 628 mg per cent per hour (normal about 16 mg per cent per hour).¹⁰ In view of the physical findings and laboratory data a diagnosis of polycythemia vera was made. There were no symptoms specifically referable to this disease, and the patient was discharged without treatment.

On August 21, 1940, she presented herself at the out-patient department complaining of a sore mouth following the extraction of a tooth three weeks previously. Examination was negative except for emaciation, a dusky skin, red mucous membranes and a palpable spleen. The red cell count was 85 million, the leukocyte count 14,900 and hemoglobin 130 per cent. At this time she refused treatment for her polycythemia.

On October 3, 1940, she again presented herself complaining of "nervousness" of six weeks' duration, an ulcer of the mouth for that length of time, and an attack of severe abdominal pain with nausea the day previous. Examination revealed an emaciated 64 year old white female who was extremely hyperkinetic. She did not remain still for longer than a few seconds but was continuously moving her arms, legs, trunk, head, and features in a variety of purposeless, irregular movements. Her speech was explosive and difficult to understand. These movements could be abolished for a moment or so on request, but would invariably return. The skin was dusky, all the superficial veins were full and prominent. The mucous membranes were red. The eyes, ears, nose and throat were negative save for a few very loose and carious teeth, and a shallow ulcer in the floor of the mouth directly under the upper right molars. This was considered to be traumatic in origin. Fundic examination revealed markedly sclerotic arteries and distended veins. The chest was clear except for an occasional crackle at the left base. Abdominal examination revealed a firm, non-tender spleen which could be palpated four fingers' breadth below the costal margin. Neurological examination revealed an extremely hyperkinetic individual. She was in almost continuous motion, her head, eyes, mouth, trunk and extremities all taking part. The movements were irregular, purposeless and at times explosive in character. Speech was infrequent, only a word or two being spoken at a time, was explosive but clearly articulated. She would quiet down remarkably when asked to do so and could even write a short sentence relatively legibly, but in a minute or so the hyperkinesis recurred. She was well oriented as to time, place and person but apparently had little insight into her condition, describing it as "nervousness". She was not unusually concerned about her activity. The cranial nerves were negative and all the deep tendon reflexes were equal, although the knee and ankle jerks were very sluggish. The abdominal reflexes were absent, there were no pathological toe signs. Sensation, so far as it could be tested, did not seem impaired. The essential laboratory data were as follows: red blood count 9.5 million, white blood count 16,500, cell volume 76 per cent, bleeding time three minutes, clotting time one minute, prothrombin time normal, sedimentation rate nil in 24 hours, clot retraction nil in 24 hours, blood sugar 98 mg per cent, non-protein nitrogen 39 mg per cent, diastase 10, blood calcium 9.5 mg per cent, phosphorus 2.9 mg per cent, potassium 25 mg per cent, total protein 8.0 per cent, A/G ratio 1.2, glycolysis rate 51.5 mg per cent per hour, spinal fluid calcium 6.5 mg per cent (normal 4.5 to 5.5) and spinal fluid protein 52 mg per cent.

Two days following admission hyperkinesis had markedly abated, though it was still apparent. Examination at this time was essentially unchanged. This state of affairs continued until the fifth hospital day when the motor phenomena reappeared in greater degree than that seen on admission. At this time, too, she could control herself for a minute or so when requested to do so. In order to prevent exhaustion, 5 c.c. of paraldehyde were administered intravenously. She slept for a few hours, but gradually the hyperkinesis reappeared and was still more exaggerated. Intravenous paraldehyde was again given, a nasal tube passed, and fluids, together with small doses of paraldehyde as needed, were given by this route. On the sixth hospital day bronchopneumonia developed. At that time neurological examination was as before save that the knee kicks and ankle jerks were absent as was also the right biceps jerk. Lumbar puncture was repeated. The spinal fluid was found to be slightly xanthochromic and contained 1000 crenated erythrocytes per cubic millimeter of fluid. Her urinary output decreased markedly. In spite of fluids administered parenterally and by nasal tube, the non-protein nitrogen rose to 85 mg per cent. Venesection produced no change in the picture, the patient getting rapidly worse and dying on the ninth hospital day.

Autopsy was performed 45 minutes after death. Aside from several small pulmonary and mesenteric thrombi the essential findings were limited to the brain. This

was of normal size and consistency and on its surface contained no hemorrhage or exudate. The cortical veins appeared dark and were distended with blood. On frontal section, throughout the brain substance the small vessels stood out prominently because their blood content was greater than normal. What appeared to be small thrombi filled many of them. These vessels stood out more prominently in the white matter, although they were present in the gray matter also. The veins within the ependyma of the lateral ventricle along the septum pellucidum were distended with blood. The ventricles were normal in size and were not distorted. The cerebellum was normal in the gross and on section. The choroid plexus of the fourth ventricle appeared hemorrhagic, and there was a small amount of bleeding into the ventricle.

Microscopic Examination In general the morphological changes were uniform throughout the sections examined. The meninges were moderately engorged and contained red cells lying free within their meshes, but no large hemorrhagic deposits. The meningeal veins, especially those of larger caliber, were engorged and some of them contained thrombi which filled their lumina. There was a rather interesting lack of uniformity in the character of the arterial structure. Many of the arteries appeared quite normal. Many, however, especially the smaller ones (those dipping into the cortex), displayed a thickening of the media without any intimal proliferation or deposits. Such vessels were scattered within the substance of the brain in various regions. The arteries did not contain thrombi. Within the brain substance, especially in the subpial and subependymal regions, there were many distended and thrombosed veins. Scattered within the substance of the brain there were smaller veins which were thrombosed and filled with rather fresh clots. Around some of these filled veins there was a variable degree of demyelination, which in some regions was rather pronounced. The basal ganglia and their surroundings shared in the same general pathological processes as described above. With hematoxylin and eosin stain no significant distortion of cortical architecture could be made out. The nerve cells had a normal structure and appearance. This applied to cortex, basal ganglia, dentate nucleus and cerebellum. No acellular areas in the cortex could be identified. Phosphotungstic acid preparations yielded no additional information regarding the general pathological picture.

COMMENT

A search of the literature has revealed four similar cases of erythremia complicated by chorea, all occurring in females. This case then represents the fifth to be reported to the present time. Of the five females three were middle-aged. The youngest was 34 years old, the oldest 78. Our patient was 64 years old. The etiology of the chorea as it complicates this disease has been thought in the past to be on a vascular basis, namely multiple cerebral thrombi. On the basis of our knowledge of central nervous system physiology chorea has generally been ascribed to some organic derangement involving the basal ganglia. However, the autopsy in this instance revealed widespread involvement of both cerebral hemispheres. The thrombi were located only in the smaller veins, and there was no predilection for these veins to be located in the basal ganglia or the area immediately adjacent. The xanthochromic and sanguinous spinal fluid obtained shortly before death was, of course, explained by the small hemorrhagic area found in the choroid plexus of the fourth ventricle at autopsy. This case was unique in that it represented the first instance reported in the literature of an autopsy performed on a person afflicted with chorea and polycythemia vera.

* * * *

Dr. Louis Turcotte assisted in the interpretation of the histological sections of the brain.

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EDITORIAL

COCCIDIOIDOMYCOSIS

THE occurrence in man of infection with the fungus *Coccidioides immitis* has been recognized since the description of the first case by Wernicke and by Posadas in Argentina 50 years ago. Many similar cases (of the generalized form of the disease) have since been reported in the United States, over 500 in all, a large majority of whom had lived in the San Joaquin Valley in California. This disease, generally known as coccidioidal granuloma, is characterized by the development of extensive granulomatous and suppurative lesions, most frequently in the lungs, but also in other viscera, in the skin, bones and joints, and occasionally in the central nervous system. Practically any tissue or organ may be involved. The lesions closely resemble those of tuberculosis in their clinical, roentgenologic and pathologic appearance. The disease usually runs a chronic progressive course, with a mortality of about 50 per cent. Coccidioidal granuloma is rare, even in the San Joaquin Valley, in which it is stated that from 40 to 50 new cases per year occur.

This was the only type of human infection recognized until 1936, when Dickson¹ and Dickson and Gifford² demonstrated that *Coccidioides immitis* was the cause of a relatively common benign disease which had long been known locally as San Joaquin Valley fever, or "desert fever." This disease is characterized by an acute onset with fever, malaise, general aches and pains, sore throat, cough, and usually scanty sputum. The latter is sometimes blood tinged and may be copious, but it often disappears after a few days. There may be a transient erythematous eruption. At the onset the infection is often mistaken for "influenza" or a severe cold, and the symptoms are frequently so mild that the patient does not come under medical observation.

After about two weeks, and often after a partial remission, characteristically a typical erythema nodosum eruption appears over the legs, more rarely on the arms, scalp, or about the neck. This may be accompanied by a recurrence of fever, and by acute joint pains and occasionally conjunctivitis. There is often a moderate leukocytosis and an eosinophilia. The eruption gradually subsides, and complete recovery nearly always occurs. This is followed by a high degree of immunity which is probably lifelong. It has been shown that the appearance of the erythema nodosum coincides with or closely follows the development of a high degree of hypersensitiveness to the fungus. The eruption is believed to be a nonspecific allergic phenomenon analogous in its pathogenesis to the similar eruption which is often observed in cases of tuberculosis.

¹ DICKSON, E. C. *Coccidioides* infection. Part I, Arch. Int. Med., 1937, lx, 1029-1044.

² DICKSON, E. C., and GIFFORD, M. A. *Coccidioides* infection (coccidioidomycosis). II. The primary type of infection, Arch. Int. Med., 1938, lxx, 853-871.

Although this eruption has been regarded as a characteristic feature of San Joaquin Valley fever and, indeed, was almost essential for its clinical recognition, it has since been shown that many similar mild primary infections with *Coccidioides immitis* occur without the eruption. In fact, the eruption appears in only from 2 per cent to 5 per cent of the cases.

Clinically the most characteristic feature of primary coccidioidomycosis is to be found in the pulmonary lesions. Abnormalities demonstrable on physical examination are variable and often trivial, but the roentgenologic changes are usually definite and fairly characteristic. These have been described by Farness and Mills,³ Winn,⁴ and others, and in this number of the *Annals of Internal Medicine* Winn and Johnson report a study of the roentgenologic changes in 40 cases of primary coccidioidal infection. This study illustrates clearly the general character of the lesions and their diversity. The resemblance to early tuberculous lesions is striking. One of the most interesting features is the early appearance of small cyst-like cavities, with little evidence of reaction on the part of the surrounding tissues, the early healing in some cases, and their persistence in others, with little tendency to progress, and with negligible effect on the general health of the patient, even though organisms are excited in abundance in the sputum.

The diagnosis depends primarily on demonstrating the organism in the sputum. This may be done by direct examination, by culture, or by animal inoculation. In the sputum (best examined in fresh moist preparations), as well as in the tissues, *Coccidioides immitis* occurs as spherical structures about 30 micra in diameter, having a thick, highly refractile cell wall. In the parasitic stage the organism reproduces by endosporulation, and the small endospores can often be seen within the spherules. There is never budding nor hypha formation. The spherules are not infectious unless actually inoculated into the tissues. On culture media (preferably Sabouraud's agar), however, hyphae grow out from these spherules, and form colonies consisting of a branching septate mycelium. Aerial hyphae grow out, and in them are produced myriads of minute chlamydospores. Local infections, however, may be acquired through skin abrasions.

The cultural and morphological characters of the organism are not entirely distinctive and positive identification requires animal inoculation, preferably intratesticular injection in guinea pigs. If either infected sputum or culture is used, after 10 days to two weeks the characteristic spherules may be formed in the tissues.

Just how and where the organism passes through this saprophytic stage under natural conditions has not been demonstrated. It has been suggested that it grows in the soil during the wet season, producing spores which are blown about in dust during the dry season. There is strong epidemiologic evidence that the infection is actually so acquired. The organism has been

³ FARNESS, O. J., and MILLS, C. W. *Coccidioides* infection, *Am. Rev. Tuberc.*, 1939, **LXXXIX**, 266.

⁴ WINN, W. A. Pulmonary cavitation associated with coccidioidal infection, *Arch. Int. Med.*, 1941, **LXXIII**, 1179-1214.

isolated from the soil as well as from small wild rodents in infested regions by Emmons⁵ and others. The number of successful isolations, however, was relatively so small (5 of 150) that it seems unlikely there can be any widespread multiplication of the organism in the soil.

A positive diagnosis of coccidioidal infection may also be made by intracutaneous tests with coccidioidin. This is a filtrate of a broth culture of the organism, analogous to tuberculin. The reaction usually becomes positive within 10 days or two weeks after infection and remains so for long periods of time, possibly throughout the life of the individual. Studies of selected groups of individuals living in regions in which the disease is prevalent, made by Smith⁶ and others, have shown a high incidence of positive reactors. Thus, in a group of 2700 school children over half gave positive reactions. Among those who had lived in the Valley less than one year, only 17 per cent gave a positive reaction, but 77 per cent of those with a residence there of more than 10 years did so. On the other hand, half of the cases showing clinical evidence of infection had lived in the Valley less than one year, and two-thirds less than two years.

Such observations indicate that in the affected regions the bulk of the population eventually becomes infected with *Coccidioides immitis* and acquires, probably, a lasting immunity. In a large majority of cases the infection is symptomless or so nearly so that it is not recognized. Most of those who show clinical evidence of infection run a benign course and recover after a few weeks. In some cases, however, the disease may run a more severe course, sometimes simulating a severe bronchopneumonia or a chronic pulmonary tuberculosis (Farness,⁷ Winn and Johnson). In only one out of several hundred cases does a general dissemination occur and the malignant form of coccidioidal granuloma develop.

The disease is not restricted to California. It is known to be prevalent in portions of Texas and Arizona, and it is probable that it will extend to other areas in the desert region, if it has not already done so. The presence of military camps in this region makes it probable that many of the men will acquire the infection and be a possible means of disseminating it widely wherever climatic conditions are such that the organism can complete the saprophytic phase of its life cycle. Thus Shelton⁸ has reported that of 736 men who gave negative coccidioidin reactions on admission to Camp Roberts, 14 reacted positively when retested three months later. Manifestly, it is important that physicians generally be aware of the existence of this disease and alert to recognize it if it should appear unexpectedly in new regions.

⁵ EMMONS, C. W. Isolation of coccidioides from soil and rodents, Pub Health Rep. 1942, LVII, 109-111.

⁶ SMITH, C. E. Epidemiology of acute coccidioidomycosis with erythema nodosum, Am Jr Pub Health, 1940, XXX, 600-611.

⁷ FARNES, O. J. Coccidioidomycosis, Jr Am Med Assoc, 1941, CXVI, 1749-1752.

⁸ SHELTON, R. M. A survey of coccidioidomycosis at Camp Roberts, California Jr Am Med Assoc, 1942, CXVIII, 1186-1190.

REVIEWS

Synopsis of Materia Medica, Toxicology and Pharmacology By FORREST RAMON DAVISON, B S , M Sc , Ph D , M B , Medical Department, The Upjohn Co Kalamazoo, Mich , formerly Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock 2nd Ed 695 pages, 13 X 20 cm C V Mosby Co , St Louis 1942

Dr Davison's book has presented a complete summary, briefly and thoroughly, on the essential use of drugs for the student of medicine and the practicing physician. Two guiding principles developed in the first edition of this book have been followed in the second edition, namely, that pharmacology is an integral part of medicine and that the study of drugs on a theoretical basis cannot be divorced from their practical application in the treatment of disease.

The author treats the principles of pharmacology, toxicology and prescription writing. The drugs are classified and a summary of materia medica is given in Part I. In Part II the subject of pharmacology is treated from the point of view of the various systems of the body on which drugs act. To illustrate, Chapter 5 in Part II deals with the drugs acting on the skin and mucous membranes, whereas Chapter XI treats drugs acting on the central nervous system, sub-heading, cerebrospinal nervous system.

The book contains numerous illustrations which are helpful in understanding the fate and action of various pharmacological agents.

After each chapter a selected bibliography follows.

The author is to be commended for his completeness in the selection of his material which makes this book a valuable addition to any physician's library.

J C K , JR

Religion in Illness and Health By CARROLL A WISE, Chaplain, Worcester State Hospital, Worcester, Mass 279 pages, 14 5 X 21 cm Harper and Bros , New York 1942 Price, \$2 50

This book is another valuable contribution to the body of literature that has been produced in recent years and that is calculated to promote better understanding and cooperation between physician and minister for the sake of the individual person who needs their combined assistance.

The author is a minister who, as Chaplain of Worcester State Hospital, has had years of training and study that well qualify him to write a most stimulating book. He is not trying to produce a superficially "popular" treatise. Neither is he a faddist. Rather he is a scientifically trained man giving a clear and careful exposition of the basic problems of human personality and its surrounding cultures that lead to illness or health. He insists that the whole person must be studied. No adequate understanding can be reached by a diagnosis of certain faulty or unhealthy parts. Man is not a mechanism but an organism and must therefore be understood as a whole.

In this process, religion has a very important part to play. Its contribution to health is primarily preventive, and secondarily curative. Religion provides insights into the nature and meaning of life. It helps men to face the facts of experience honestly and rightly. It creates more integrated, and thus more healthy, personalities.

This is a good book. It ought to be helpful to doctors, but even more so to ministers and social workers. Like the First Aid courses given by the Red Cross, it shows some of the damage that clergymen and others can do to the health of people.

It warns them of some things not to do But best of all, it furnishes a basis for expanding thought and deepening understanding of human beings and their needs
T G S

Wounds and Fractures By H WINNETT ORR, M D , F A C S 227 pages, 16 5
X 26 cm Charles C Thomas, Springfield, Illinois 1941 Price, \$5 00

The work, "Wounds and Fractures" by H Winnett Orr, is a tribute to the surgical skill of an exceptional man, but the author fails to realize that methods which are simple to him may be impossible for others less gifted to carry out

He emphasizes early treatment of fractures and will accept nothing but the best possible position and fixation Good surgery is demanded as a preliminary to successful (Orr method) infrequent dressing routine It is refreshing to find one brave enough to treat wounds without once mentioning sulfonamides, which reiterates that good surgery is still at a premium He has given little space to wounds not associated with fractures

The author criticizes many accepted methods without satisfactory explanation He decries a method of pin fixation in common use, which, however, is much like his own He speaks lightly of shock and gas bacillus infection

Certain chapters describe his methods too briefly, but the style is graceful, making reading easy and rapid The book will be enjoyed by all interested in this field of surgery, and many axioms will be remembered

O C B

COLLEGE NEWS NOTES

SUPPLEMENTARY LIST OF MEMBERS OF THE AMERICAN COLLEGE OF PHYSICIANS

On Active Military Duty

In the July, 1942, issue of this Journal there appeared a list of the members of the American College of Physicians who up to that time were known to be on active military duty. Since that time we have had reports that the following Fellows and Associates have been called to active duty with the armed forces of their country.

Maurice J. Abrams
Jacques H. Ahronheim
William W. Alexander
Edgar V. Allen
Frank J. Altschul
Charles H. Armentrout
Dudley C. Ashton
Harold C. Atkinson

James P. Baker
Gordon W. Balyeat
Joseph Bank
Walter Bauer
Abraham Becker
Julien E. Benjamin
Clifton H. Berlinghof
Michael Bevilacqua
Earl J. Bieri
Samuel Blackwell
Franklin B. Bogart
Francis J. Braceland
Charles A. Breck
Hugh R. Butt
Charles S. Byron

John W. G. Caldwell
Donald C. Campbell
Louie T. Carl
Henry R. Carstens
Charles R. Castlen
William Chester
H. Dumont Clark
Thomas A. Clawson, Jr.
James H. Closson
Charles B. Coggin
Leon H. Collins, Jr.
Ralph R. Cooper
Darrell C. Crain
George W. Cramp
Robert W. Currie
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Edward H. Cushing
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Alva D. Daughton
Marion T. Davidson
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Thomas N. Horan
Arthur J. Horton
George H. Houck
Albert S. Hyman

Irving R. Juster

Mennasch Kalkstein
John L. Kantor
T. Douglas Kendrick
Francis E. Kenny
Otis G. King
J. Murray Kinsman

Michael Lake
John E. Leach
Edward P. Leeper
Charles E. Lemmon

Jerome S Levy
 Bernard I Lidman
 McKinley London
 William S Love, Jr

Thomas T Mackie
 Emory H Main
 Orlando B Mayer
 Jesse McCall
 Harold P McGan
 Perry J Melnick
 Ralph W Mendelson
 Harold R Merwarth
 James C Metts
 Frank Meyers
 Solomon G Meyers
 Earl L Mills
 Morris E Missal
 Matthew Molitch
 Bert E Mulvey
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 Sam A Overstreet

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 Morton M Pinckney
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 Alvin E Price

Jack O W Rash
 Joseph W Rastetter
 Walter G Reddick
 Arthur J Revell

Stephen Reynolds
 Rafael Rodriguez-Molina
 Paul B Roen
 Jack Rom
 Thomas L Ross, Jr
 Chauncey L Royster
 Hendrik M Rozendaal

Henry A Schroeder
 Leon Schwartz
 Maurice M Scurry
 Loyd W Sheckles, Jr
 Karl Shepard
 Euclid M Smith
 Wilson F Smith
 Edward D Spalding
 Gilbert M Stevenson
 Lewis T Stoneburner, III

Elam C Toone, Jr
 James H Townsend
 Woodford B Troutman
 Pat A Tuckwiller
 Arthur R Twiss

William G Ure

John Vaughn

Emmett D Wall
 James A Walsh
 Charles H Watkins
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 Dr James R Lisa, F A C P , New York, N Y —15 reprints,
 Dr Aaron E Parsonnet, F A C P , Newark, N J.—1 reprint,
 Dr Emilie V Rundlett, F A C P , Jersey City, N J —1 reprint,
 Dr John H Shaffer, F A C P , Detroit, Mich —1 reprint,
 Dr Hugh Stalker, F A C P ; Detroit, Mich —3 reprints,
 Ralph M Thompson, F A C P , Lieutenant Colonel, (MC), U S Army—1 reprint,
 Dr Stuart L Vaughan, F A C P , Buffalo, N Y —1 reprint,
 Leon H Warren (Associate), Major, (MC), U S Army—12 reprints,
 Dr John W Williams, F A C P , Cambridge, Mass —32 reprints

Dr Louis L Perkel, F A C P , Jersey City, N J , has donated a personally executed photograph entitled "Grand Central" to the College Headquarters This work was exhibited at the recent meeting of the American Physicians' Art Association

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows

AMERICAN BOARD OF INTERNAL MEDICINE

William A Werrell, M D , Assistant Secretary
 1301 University Ave
 Madison, Wis

Written Examinations Will be given in various centers October 19, 1942
 Applications must be filed before September 1, 1942

Oral Examinations Philadelphia, Pa , April, 1943, in advance of the meeting of the American College of Physicians, San Francisco, Calif , 1943, in advance of the meeting of the American Medical Association

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY

C Guy Lane, M D , Secretary
 416 Marlboro St
 Boston, Mass

Written Examinations Will be given in various centers, October 12, 1942

Oral Examinations Chicago, Ill , December 4-5, 1942

AMERICAN BOARD OF PATHOLOGY

F W Hartman, M D , Secretary
 Henry Ford Hospital
 Detroit, Mich

Written and Oral Examinations Richmond, Va , November 9-10, 1942

AMERICAN BOARD OF PEDIATRICS

C A Aldrich, M D , Secretary
 707 Fullerton Ave
 Chicago, Ill

Oral Examinations Chicago, Ill , November 1-3, 1942, in advance of the meeting of the American Academy of Pediatrics, New York, N Y , December 4-6, 1942

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

Walter Freeman, M D , Secretary
 1028 Connecticut Ave , N W
 Washington, D C

Oral Examinations New York, N. Y , December, 1942, San Francisco, Calif , June, 1943

AMERICAN BOARD OF RADIOLOGY
B R Kirklin, M D , Secretary
Mayo Clinic
Rochester, Minn

Oral Examinations Chicago, Ill , Novem-
ber 27-29, 1942

For further details and application forms communicate with the respective secretaries

ACTING GOVERNORS OF THE COLLEGE APPOINTED FOR
MINNESOTA AND EASTERN PENNSYLVANIA

Dr Edgar V Allen, Rochester, Minn , College Governor for that State, has, as of August 1, entered the Medical Corps of the U S Army as a Lieutenant Colonel, as Consultant in Medicine and Coordinator of Professional Service for the 7th Corps Area Dr E H Ryneanson of Rochester, Minn , has been appointed Acting Governor for Minnesota to serve until such time as Governor Allen may return

As of August 1, Dr Edward L Bortz, Philadelphia, Governor for Eastern Pennsylvania, who is a Lieutenant Commander in the Medical Corps of the U S Navy, has been transferred from the Philadelphia Naval Hospital, and Dr Thomas M McMillan, 2044 Locust Street, Philadelphia, has been appointed Acting Governor by the Executive Committee of the College Dr McMillan will serve during Dr Bortz's absence

Dr LeRoy H Sloan, F A C P , College Governor for Northern Illinois, has been elected President of the Chicago Society of Internal Medicine Dr Italo Volini, F A C P , was elected Vice President, and Dr Richard Capps (Associate), was elected Secretary Dr Capps is now on active military duty with the Northwestern University Unit, and during his absence Dr Howard Alt will act as Secretary Pro Tem

Dr Barnett Greenhouse, F A C P , New Haven, Conn , has been appointed Consultant in Medicine to the Griffin Hospital, Derby, Conn

Dr Robert H Felix, F A C P , U S Public Health Service, has been assigned to the U S Coast Guard Academy, New London, Conn , which is a training school for officers of the Coast Guard Dr Felix will be in charge of organizing, developing, and administering a psychiatric service for the cadets at the Academy

Dr Charles G Sinclair, F A C P , has been advanced from Lieutenant Colonel to Colonel in the Medical Corps of the U S Army, and has been assigned as Camp Surgeon and Commanding Officer of the Station Hospital, Camp Hood, Tex

Dr J C Geiger, F A C P , Director of Public Health of the City and County of San Francisco, was awarded the blue ribbon and collar of the Order of Merit, Grade of Commander, by the Government of the Republic of Chile, for "excellence of administration and research in solving public health problems "

The Alumnae Association of the Woman's Medical College of Pennsylvania, Philadelphia, held its 67th Annual Meeting, June 2, 1942 At a scientific session of this meeting, Dr Mary M Spears, F A C P , Philadelphia, Pa , spoke on "Diagnosis of Lesions of Lower Colon," and Dr Frieda Baumann, F A C P , Philadelphia, Pa , spoke on "The Chemical Aspects of the Sulfa Drugs " Dr Ellen C Potter, F A C P , Trenton, N J , Acting President of the College, presented a report of the Board of Corporators to the Association

At a recent meeting of the Arizona State Medical Association in Prescott, Dr Virgil G Presson, F A C P , Tucson, was chosen Vice President and Dr William W Watkins, F A C P , Phoenix, was reelected Secretary

Dr Percy T Magan, F A C P , has retired as President and Professor of Medical Ethics at the College of Medical Evangelists, Los Angeles, Calif Dr Magan was the guest of honor at a reception in Los Angeles, May 13, held by students, alumni, and friends to mark his retirement as President of the College

Dr Walter E Macpherson (Associate), Los Angeles, Calif , Professor of Internal Medicine and Physiology at the College, has been named President succeeding Dr Magan

Dr Josiah J Moore, F A C P , Chicago, Ill , has been elected President of the Society of Illinois Bacteriologists

Dr Stanley G Wolfe, F A C P , Shreveport, was installed as President of the Louisiana State Pediatric Society at its recent meeting

Dr Kennon Dunham, F A C P , Cincinnati, was reelected President of the Ohio Public Health Association at its annual meeting in Columbus, May 21, 1942

Dr Abraham H Aaron, F A C P , Buffalo, N Y , spoke on "Important Medical Measures in the Management of Gastrointestinal Diseases" at a joint meeting of the Third and Twelfth Councilor Districts of the Medical Society of the State of Pennsylvania in Sayre, June 24

Dr Baldwin L Keyes, F A C P , has been named Professor of Psychiatry, Dr Martin E Rehfuss, F A C P , Sutherland M Prevost Lecturer in Therapeutics in the Department of Medicine, Dr Garfield G Duncan, Clinical Professor of Medicine at the Jefferson Medical College of Philadelphia

Dr Walter E Vest, F A C P , Huntington, W Va , has been elected President of the American Therapeutic Society, and Dr Oscar B Hunter, F A C P , Washington, D C , has been reelected Secretary

Dr Eugene M Landis, F A C P , Charlottesville, Va , has been elected President of the American Society for Clinical Investigation, and Dr Wesley W Spink, F A C P , Minneapolis, Minn , Secretary

Dr James E Paullin, F A C P , Atlanta, Ga , President of the College, was honored at a dinner, July 7, given by the Fulton County (Ga) Medical Society to mark his election as President-Elect of the American Medical Association

Dr Harold C Ochsner, F A C P , Indianapolis, has been named Secretary-Treasurer of the Indiana Roentgen Society

Dr William Dameshek, F A C P , has been appointed Professor of Clinical Medicine at Tufts College Medical School, Boston, Mass

Dr Roger I Lee, F A C P , Boston, Mass , was chosen President-Elect of the Massachusetts Medical Society at its annual meeting in Boston, May 25, 1942

Dr Franklin H Top (Associate), has been named Medical Director of the Herman Kiefer Hospital, Detroit, Mich

Dr Thomas A Lebbetter, F A C P , Yarmouth, Nova Scotia, a Lieutenant Colonel in the Medical Corps of the Royal Canadian Army, is now attached to Army Headquarters at Ottawa as Assistant Adjutant General

At the annual meeting of the North Dakota State Medical Association in Jamestown, May 18-20, 1942, Dr Gordon R Kamman, F A C P , St Paul, Minn , spoke on "The Depressed Patient," and Dr Arthur C Fortney, F A C P , Fargo, N D , and Dr Paul J Breslich, F A C P , Minot, N D , were among those who conducted a symposium on "Encephalomyelitis "

At the annual meeting of the Texas State Heart Association in Houston, May 11, Dr Marvin L Graves, F A C P , Houston, was elected President, Dr Merritt B Whitten (Associate), Dallas, Vice President, and Dr Walter B Whiting, F A C P , Wichita Falls, Secretary-Treasurer

Dr Roy L Leak, F A C P , Middletown, has been named President of the Connecticut State Medical Society

At the recent annual meeting of the Radiological Society of New Jersey, Dr Harry J Perlberg, F A C P , Jersey City, was named Secretary

Dr Roy R Snowden, F A C P , College Governor for Western Pennsylvania, Pittsburgh, spoke on "Recent Advances in Our Knowledge of Hypertension" at a meeting of the Eighth Councilor District of the Medical Society of the State of Pennsylvania in Conneaut Lake, July 15.

Dr Daniel P Griffin, F A C P , Bridgeport, was elected President of the Connecticut Society for Psychiatry and Neurology at its recent annual meeting

Dr Paul P McCain, F A C P , Superintendent of the North Carolina Sanatorium for the Treatment of Tuberculosis at Sanatorium and the Western North Carolina Sanatorium at Black Mountain, has been named Superintendent of the Eastern North Carolina Sanatorium now under construction in Wilson

Dr David W Baird, F A C P , Associate Dean and Associate Clinical Professor of Medicine at the University of Oregon Medical School, Portland, has been appointed Acting Dean of the Medical School

Among the speakers at a meeting of the Fifth Councilor District of the Medical Society of the State of Pennsylvania, July 9, in Harrisburg, were

Dr Harry B Thomas, F A C P , York—"Practical Problems in Diabetes".

Charles R Reynolds, F A C P , Major General, (MC), U. S Army (Retired)—
"Tuberculosis in the War",
Dr Edward L Bortz, F A C P , Philadelphia—"New Light on Old Folks "

At a meeting of the North Texas Medical Association in Terrell, June 2, Dr George R Herrmann, F A C P , Galveston, spoke on "Interpretation of Electrocardiogram and Coronary Artery Disease," and Dr Milford O Rouse, F A C P , Dallas, spoke on "Diagnosis and Medical Management of the Gallbladder "

The American Dietetic Association will hold its twenty-fifth annual meeting at the Hotel Statler in Detroit on October 19 to 22

TUBERCULOSIS INCREASES IN GREAT BRITAIN

Recent announcements by William H Stoneman of the Medical Research Council indicates a sharp rise in the incidence of tuberculosis in Great Britain, with an increase in deaths from both pulmonary and nonpulmonary types since the beginning of the war Between 1939 and 1940 deaths from pulmonary tuberculosis increased 6 per cent and in 1941 there was an additional 10 per cent increase over 1939 Even a greater increase in the percentage of deaths from nonpulmonary tuberculosis occurred There was a 40 per cent increase between 1939 and 1941 in deaths from tuberculosis meningitis The increase in the tuberculosis death rate, except for the increase of 34 per cent between 1939 and 1941 in venereal diseases, is the most significant threat in the wartime health situation of England

Various causes have been advanced such as the increased use of unpasteurized milk, the closing of sanatoria, releasing carriers, a general decrease in physical resistance due to long working hours and unsatisfactory diet, the difficulty in providing regular treatment because of the shifting of infected people who are still working, increased numbers of contacts with active carriers, and lack of facilities for proper treatment

It has been pointed out that thus far there have been no widespread epidemic diseases as had been expected, and furthermore, that in the case of some diseases, which were expected greatly to increase during the war, there has actually been a marked decrease, both in incidence and in percentage of fatal cases

F A C P 'S BECOME OFFICERS, MONTANA STATE MEDICAL ASSOCIATION

At the 64th Annual Meeting of the Montana State Medical Association in Missoula, Mont , July 8-10, 1942, Dr Ernest D Hitchcock, F A C P , College Governor for Montana, of Great Falls, was inducted as President, Dr J P Ritchey, F A C P , Missoula, was elected President-Elect, and Dr Thomas F Walker, F A C P , Great Falls, was elected Secretary

Dr Walter L Nalls, F A C P , Richmond, was recently elected Secretary-Treasurer of the Society of Chest Physicians of Virginia

MISSISSIPPI VALLEY MEDICAL SOCIETY TO MEET IN QUINCY, ILLINOIS, SEPTEMBER 30-OCTOBER 2

The 8th Annual Meeting of the Mississippi Valley Medical Society, under the Presidency of Dr Dan G Stine, F A C P , Columbia, Mo , will be held at the Hotel

Lincoln-Douglas, Quincy, Ill, September 30–October 2, 1942 About twenty-five clinician-teachers will present a program of lectures, demonstrations, and instructional courses

On September 30 the courses will be given by a group of Kansas City, Mo, and Rochester, Minn, clinicians, among whom are Dr Graham Asher, F A C P, Kansas City, on "Clinical Factors Which Influence Digitalis Administration" and Dr Russell M Wilder, F A C P, Rochester, Minn, on "Insulin in the Treatment of Diabetes" and "Food Control for Public Health Nutritional Considerations" On October 1 Chicago clinicians will be in charge, among whom will appear Dr Robert A Black, F A C P, on the subject of "Rheumatic Heart Disease in Children" For October 2 the following are among those on the program Dr James H Hutton, F A C P, Chicago, on "Endocrine Diagnosis and Treatment from the Clinician's Standpoint" and Dr Arthur L Smith, F A C P, Lincoln, Nebr, on "Treatment of Heart Emergencies with Reproduced Heart Sounds"

MEDICAL EDITORS TO MEET AT QUINCY, ILL, SEPTEMBER 30

The 2nd Annual Meeting of the Mississippi Valley Medical Editors' Association will be held at the Hotel Lincoln-Douglas, Quincy, Ill, Wednesday, September 30 This will be a dinner meeting under the leadership of Dr Clyde P Dyer, of St Louis, Editor of the St Louis County Medical Bulletin and President of the Association The meeting is being held during the 8th Annual Meeting of the Mississippi Valley Medical Society, which will also meet at the Hotel Lincoln-Douglas, September 30, October 1, 2 All past and present medical editors and those interested in medical journalism or writing are cordially invited to attend There is no registration fee Program of the meeting or dinner reservations may be secured through Harold Swanberg, M D, F A C P, Secretary of the Association, W C U Building, Quincy, Ill

The Health Supplies Branch of the War Production Board has again called attention to the fact that all stocks of Quinine and Totaquine, no matter how small, have been subject to the restrictions of Conservation Order M-131 since June 19, 1942 These products may not be sold for any purpose except as an anti-malarial agent The order extends to powder, capsules, solutions, pills and tablets and to Quinine or Totaquine stocks of all other descriptions whether or not packages have been opened

The same restrictions apply to Cinchonine, Cinchonidine and Quinidine, except that Quinidine may be sold for the treatment of cardiac disorders These restrictions are necessary because these drugs are urgently needed for military use Supplies are limited since the raw material, cinchona bark, comes in most part from Java The restrictions extend not only to the sale of these products by retail druggists but to dispensing of these drugs on physicians' prescriptions

CALENDAR OF POSTGRADUATE COURSES AVAILABLE AT TUFTS MEDICAL SCHOOL

Boston, Mass

During 1942–43

The following courses are designed for the busy general practitioner who wishes to bring his knowledge up to date The courses are all under the auspices of Tufts Medical School, and will largely be given in the New England Medical Center (Boston Dispensary, Joseph H Pratt Diagnostic Hospital, Boston Floating Hospital and Tufts Medical School)

Admission Graduates of approved medical schools are eligible. They should submit evidence of membership in their State medical societies. Applications should be made to the Chairman, Postgraduate Division, Tufts Medical School, 30 Bennet St., Boston, Mass.

Fees In addition to the tuition fees indicated, a \$5.00 registration fee shall be paid, which covers any courses taken at this institution within a twelve-month period.

Electrocardiography

September 28–October 2, 1942, also, May 10–14, 1943

Fee, \$25.00

Demonstrations and intensive study of records, present status of electrocardiogram interpretation in coronary disease, arrhythmias, syphilitic, congenital and rheumatic heart disease, myxedema, pericarditis, etc. Drs. Heinz Magendantz, Samuel Proger and Associates.

Internal Medicine

October 5–30, 1942, also, May 3–28, 1943

Fee, \$50.00

Ward rounds and staff conferences in the Joseph H. Pratt Diagnostic Hospital, examination of patients in the different medical clinics of the Boston Dispensary, informal discussions with chief technicians of pathology, bacteriology and chemistry laboratories, followed by lectures by physicians on their various specialties, such as hematology, neurology, gynecology, allergy, cardiology, endocrinology, nephritis and hypertension, spleen and liver diseases, etc. Dr. Samuel Proger in charge.

Endocrinology

November 9–13, 1942, also, May 24–28, 1943

Fee, \$25.00

A course intended to clarify more recent advances in this field, stressing their clinical application, demonstrations of tests and laboratory methods, attendance at the Boston Dispensary Endocrine Clinics, lectures and conferences, ward rounds and examination of patients. Dr. Charles H. Lawrence in charge.

Hematology A

November 16–21, 1942

Fee, \$25.00

Conferences and laboratory and clinical work at Pratt Diagnostic Hospital and Boston Dispensary, case presentations and lectures on bone marrow, anemia, leukopenic disorders, leukemia, bone marrow biopsy, etc. Drs. Heinrich Brugsch and William Dameshek.

Cardiology

November 16–21, 1942, also, May 3–8, 1943.

Fee, \$25.00

Practical application of present-day knowledge of heart disease, therapy of heart disorders, daily lectures followed by pathological demonstrations and case presentations. Dr. Samuel Proger in charge.

Pediatrics

January 4–30, 1943

Fee, \$50.00

Daily ward rounds in the Boston Floating Hospital and examination of patients on the wards of the Floating Hospital and in the Children's Clinics of the Boston Dispensary. Afternoon visits to South Department of the Boston City Hospital, the Diabetes Clinic of the New England Deaconess Hospital, the Evangeline Booth Hospital and the Chapin Hospital in Providence, R. I., where contagious diseases, diseases of the newborn, prematurity and diabetes will be taken up. Enrollment limited to four. Dr. James Marvin Baty in charge.

Radiology

January 12-15, 1943

Fee, \$25 00

General practitioner's course, x-ray interpretation in diseases of the heart, gastrointestinal tract and bone, in obstetrical cases, and in diseases of children
Dr Alice Ettinger in charge

Dermatology B

January 18-23, 1943

Fee, \$25 00

Mornings at the Skin Clinic of the Boston City Hospital and in the Syphilis Clinic, afternoon lectures, demonstrations and discussions Dr William P Boardman in charge

Diabetes

January 18-23, 1943

Fee, \$25 00

A study of the clinical methods and procedures most effective in the diagnosis and treatment of diabetes mellitus and its complications Dr Joseph Rosenthal in charge

Advanced Electrocardiography

January 25-27, 1943

Fee, \$20 00

A three-day continuation course planned especially for those who have taken the preliminary course, or who have had sufficient experience in the interpretation of electrocardiograms Dr Heinz Magendantz in charge

Gastro-Enterology

February 8-13, 1943

Fee, \$25 00

Review of modern methods, their importance in diagnosis and treatment and their limitations, systematic discussion of diagnosis, treatment and complications of the commoner gastro-intestinal diseases Dr Katherine S Andrews in charge

Dermatology A

May 17-22, 1943

Fee, \$25 00

A highly concentrated course discussing from the practical standpoint the diagnosis and therapy of the commoner diseases of the skin Dr Francis M Thurmon in charge

Allergy

October 19-23, 1942, and May 17-21, 1943

Fee, \$25 00

Present-day status of the diagnosis and treatment of allergic conditions, lectures on hayfever, bronchial asthma, atopic eczema, urticaria, serum disease, histamine and the pharmacology of allergic diseases, clinic demonstrations at Boston Dispensary Dr Ethan Allan Brown in charge

Hematology C

July 5-17, 1943

Fee, \$75 00

An intensive course, lectures, informal discussions, laboratory and bedside teaching Dr William Dameshek in charge

OBITUARIES

DR WILLIAM McCULLY JAMES

Dr William McCully James, former Governor of the College, died of a cerebral hemorrhage on July 10, 1942, at the age of 62 years, at the Panama Hospital

Dr James was born May 29, 1880, at Richmond, Virginia. He took his premedical training at Johns Hopkins University, and graduated in Medicine from the Medical Department of the University of Virginia, in 1906. He came to the Isthmus immediately after graduation, and interned at Colon Hospital, later serving at Ancon (now Gorgas) Hospital, where he was assistant to the Chief of the Medical Service from 1910 to 1914, and then as District Physician at Ancon, Canal Zone. He left the Government service in 1916 to join with Dr A. B. Herrick and Dr D. F. Reeder in establishing the Panama Hospital and Herrick Clinic, of which he was Chief of the Medical Service until his death. During the first World War, he served as a Major in the Medical Corps of the United States Army, and was later commissioned a Lieutenant-Colonel in the Medical Reserve Corps. He was a Colonel in the Panamanian Army during the border dispute with Costa Rica in 1921. He was for many years Consultant in Tropical Medicine to the United Fruit Company.

He was always an ardent and untiring student, and soon became recognized as an authority on tropical diseases, especially malaria and amebiasis, on which he published numerous papers, including a monograph on the Etiology and Treatment of Hemoglobinuric Fever in the Canal Zone, written in collaboration with Dr W. E. Deeks, and published by the Department of Sanitation of the Isthmian Canal Commission, and a monograph on a Study of the Entamoebae of Man in the Panama Canal Zone, published in the Annals of Tropical Medicine and Parasitology (Liverpool). In 1912, he prepared an exhibit on malaria and dysentery for the Department of Sanitation of the Isthmian Canal Commission, which was awarded a Certificate of Honor at the Atlantic City Convention of the American Medical Association. An exhibit on amebiasis, prepared in collaboration with Drs L. B. Bates, Lawrence Getz, and J. J. Vallarino, was awarded a Bronze Medal at the Washington Convention in 1927, and in 1934, at the Cleveland Convention, with Drs Bates, Getz, and Icaza, he was awarded the Class II Gold Medal for a complete and detailed exhibit on the pathology of amebiasis.

He was a fellow of the American Medical Association and Southern Medical Association, a charter member and eighth president of the Medical Association of the Isthmian Canal Zone, a charter member and past first vice president of the National Medical Association of Panama, a charter member of the American Society of Tropical Medicine, a member of the American Society of Parasitologists, an honorary member of the National

Gastro-enterological Association, a fellow of the Royal Society of Tropical Medicine and Hygiene, and of the Royal Microscopical Society, an associate member of the Medical and Surgical Society of Guayaquil, Ecuador, an honorary member of the Rafael Calvo Society of Cartagena, Colombia, and a Diplomate of the American Board of Internal Medicine. He was a Fellow of the American College of Physicians since 1926, and Governor for Panama and the Canal Zone from 1928 to 1941.

He was a member of Kappa Alpha and Phi Rho Sigma fraternities, and of Phi Beta Kappa and Alpha Omega Alpha honorary fraternities, a thirty-third degree Mason, member of the Scottish and York Rite Bodies, and Noble of the Mystic Shrine. He was for many years, a member of the Cosmos Club, of Washington, and of the Union Club and Golf Club, of Panama. He was a founder and past president of the American Society of Panama, and a member of the American Legion and Rotary Club. The Republic of Ecuador decorated him with the Order of Merit, and the Republic of Panama with the Order of Vasco Núñez de Balboa.

Dr James' death was a great loss to the Isthmian community, and to the medical profession. He was an eminent physician, whose ability, sympathetic understanding, and great personal interest in all his patients, won him thousands of devoted friends, from all parts of the Isthmus and Central America. He did much to promote friendship and understanding between the American and Panamanian communities. He was honest, loyal, unselfish, and deeply devoted to his profession. He had an outstanding personality, and was an important part of Isthmian life. Panama and the Canal Zone will not be the same without "Dr James."

He is survived by his wife, Mrs Mary James, a daughter, Mary Celeste, and a brother, Alfred.

GILBERT M. STEVENSON, M.D., F.A.C.P.,
Governor for Panama and the Canal Zone

DR LOUISE TAYLER JONES

It is with a deep sense of sorrow and a keen feeling of personal loss that we record the death on December 21, 1941, of Dr Louise Tayler Jones.

She lived a full life and her talent was often devoted to the service of people in distant lands.

In her later years it was our good fortune to have her live among us and to enrich our meetings by her presence. To recount the details of her life, to list the numerous honors that came to her, do not portray the character and the charm of personality of this distinguished woman and physician.

Born in Youngstown, Ohio, November 14, 1870, she received her A.B. degree from Wellesley College and an M.S. from George Washington University. In 1903 she graduated in Medicine from the then young Johns Hopkins University School of Medicine, and, following this, interned at the Babies' Hospital in New York. During 1907 and 1908 she was acting phy-

sician in charge at this Hospital Following this she located in Washington and there devoted much of her time and energy to welfare work During her years in Washington she served as Pediatrician to the Florence Crittenden Home and to the Columbia Hospital She was an Associate at the Children's Hospital and Chief of the Child Welfare Clinic

Her services during the first World War were outstanding During 1915 she was Director of the American Red Cross in Serbia, and during 1919 she served with the Wellesley and American Women's Hospital Units in France

Dr Jones was a member of the District of Columbia Medical Society, serving a term as Vice-President She was also a member of the Women's Medical Society of the District of Columbia, the American Academy of Pediatrics, the Medical Women's National Association, of which she was President from 1928 to 1929 She was Vice-President of the Medical Women's International Association from 1929 to 1934, and President of the Washington Branch of the American Association of University Women from 1923 to 1924 She was a member of the American Medical Association, and a Fellow of the American College of Physicians since 1926

We of her adopted State look upon this list of honorable achievements as a fitting symbol of her worth, and we remember them with pride; but we remember her not only as an accomplished physician but also as a very gracious woman

WALTER B MARTIN, M D, F A C P,
Governor for Virginia

DR GEORGE FORBES

Dr George Forbes was born in Brooklyn, N Y, on November 5, 1867, and died at his home on June 23, 1942, of cancer of the colon He received his M D degree from New York University Medical College in 1890 His early medical career was devoted to general practice In 1898 he became interested in x-ray work and gradually gave more of his time to this specialty until 1915 when he limited his practice to roentgenology

Dr Forbes was Director of Roentgenology at St Johns Hospital, Long Island City, 1904 to 1939, St Catherine's Hospital, Brooklyn, 1914 to 1936, Roosevelt Hospital, New York City, 1916 to 1923, Wyckoff Heights and Bethany Deaconess Hospitals, Brooklyn, 1917 until his death

He became a Fellow of the American College of Physicians in 1920 He was a charter member of the Radiological Society of North America, and a member of the Kings County Medical Society and the American Medical Association

On April 10, 1940, over 400 of his friends, colleagues and former patients gave him a testimonial dinner at Essex House in New York City to honor him on the completion of fifty years of practice

Dr Forbest leaves a widow, the former Norene Cadmus, to whom he was married in 1891, one son, three daughters and seven grandchildren.

DR PERCIVAL GORDON WHITE

With the untimely passing of Dr Percival Gordon White in Los Angeles on April 28, another breach has been made in the ranks of medical men of the old school Dr White was a man to whom the honest practice of medicine was the most important thing in life He never spared himself at the expense of any patient, rich or poor, and in fact he well might be alive today had he given more consideration to his own health and less to that of others, following his first coronary attack

The son of a Lieutenant-Colonel in the British army, Dr White was born in Woodstock, Ontario He received his earlier education at the Woodstock Collegiate School and his medical degree from McGill University Faculty of Medicine, Montreal He came to Los Angeles in 1910 and after the first World War broke out went overseas as a Major in the U S Army Medical Corps and was in charge of an evacuation hospital in France for a year On his return to Los Angeles he renewed his former association with Dr M L Moore and Dr E C Moore, a partnership which later resulted in the foundation of the well-known Moore-White Clinic, in the work of which Dr White was active until his final illness He was a member of county and state societies, a Fellow of the American Medical Association and a Fellow of the American College of Physicians

Dr White was a man who stood very high in the profession He possessed unmistakably those qualities which are the natural inheritance of the born doctor The human element never was missing in his contact with his patients, and this, coupled with his fine medical ability, his humor, and his kindness in his personal relations made of him a man esteemed for himself and highly respected for his professional skill The medical profession could well do with more men of the calibre of Dr Percy White

Dr White is survived by his widow, Jessie R White, a brother and sister in Canada and hundreds of friends by whom his name will not be forgotten

ROY E THOMAS, M D, F A C P,
Governor for Southern California

DR HAROLD G F EDWARDS

Dr Harold G F Edwards was born in Abbeville, Louisiana, November 18, 1888 He received his primary education in the public schools of Abbeville, his premedical education in Jefferson College at Convent, Louisiana, and received an M D degree from Tulane University in 1911 Prior to his entering Tulane University he was for a time editor of the Abbeville *Herald* After practicing medicine in Abbeville for several years, Dr Edwards enlisted in the United States Army Medical Corps in 1917, in which he attained the rank of captain before his honorable discharge in 1919

Following his discharge from the Army Dr Edwards received post-graduate training in radiology at Bellevue Hospital, New York, and Cook

County Hospital in Chicago. He served as radiologist in the St. John's Hospital, Lafayette, Louisiana, from 1922 to 1928. In 1928 he removed to Shreveport, Louisiana, where he practiced radiology until his death. He was radiologist to the Willis Knighton Clinic and the Tri-State Hospital from 1930 to 1931, Director of the Tumor Clinic, Shreveport Charity Hospital, from 1932 to 1940, and Director of the X-ray Department, Shreveport Charity Hospital, from 1935 to 1940.

He held membership in the Radiological Society of North America, the American Radium Society, and the American College of Radiology. He had been President of the Third District Medical Society of Louisiana, and Secretary and later President of the Louisiana State Radiological Society. He became a Fellow of the American College of Physicians in 1929.

Dr. Edwards' principal interests and principal contributions to medical science were in the field of x-ray and radium therapy. Throughout the South he was recognized as an authority on these subjects, and made numerous contributions to the literature.

Dr. Edwards died May 2, 1942, of coronary occlusion.

EDGAR HULL, M D , F A C P ,
Governor for Louisiana

MINUTES OF THE BOARD OF GOVERNORS

ST PAUL, MINN

April 20, 1942

The first meeting of the Board of Governors, in conjunction with the Twenty-sixth Annual Session of the American College of Physicians, convened in the Municipal Auditorium, St Paul, Minn, Monday, April 20, 1942, at 5 p m, Chairman Charles H Cocke presiding and Executive Secretary E R Loveland acting as Secretary

Secretary Loveland called the roll and the following responded (Those marked with an asterisk were alternate Governors serving in the place of the regular Governors who were absent)

Oliver C Melson	ARKANSAS
Fred M Smith	IOWA
*Edgar Hull	LOUISIANA
Henry R Carstens	MICHIGAN
Edgar V Allen	MINNESOTA
A Comingo Griffith	MISSOURI
*Harry T French	NEW HAMPSHIRE
George H Lathrope	NEW JERSEY
Charles H Cocke	NORTH CAROLINA
*L H Fredericks	NORTH DAKOTA
Alexander M Burgess	RHODE ISLAND
*L E Madden	SOUTH CAROLINA
Paul K French	VERMONT
Walter B Martin	VIRGINIA
*E G Bannick	WASHINGTON
Albert H Hoge	WEST VIRGINIA
*J H Watkins	ALABAMA
Lewis B Flinn	DELAWARE
Turner Z Cason	FLORIDA
LeRoy H Sloan	NORTHERN ILLINOIS
C W Dowden	KENTUCKY
Eugene H Drake	MAINE
Louis Krause	MARYLAND
John G Archer	MISSISSIPPI
Ernest D Hitchcock	MONTANA
*Irving S Wright	EASTERN NEW YORK
A B Brower	OHIO
Homer P Rush	OREGON
M D Levy	TEXAS
Elmer L Sevringhaus	WISCONSIN
Ramon M Suarez	PUERTO RICO
George F Strong	ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN
Roy E Thomas	SOUTHERN CALIFORNIA
James J Waring	COLORADO
*J S Nickum	CONNECTICUT
Wallace M Yater	DISTRICT OF COLUMBIA
Cecil M Jack	SOUTHERN ILLINOIS
Robert M Moore	INDIANA

Harold H Jones	KANSAS
Warren Thompson	NEBRASKA
Nelson G Russell, Sr	WESTERN NEW YORK
Leander A Riely	OKLAHOMA
Edward L Bortz	EASTERN PENNSYLVANIA
*L D Sargent	WESTERN PENNSYLVANIA
John L Calene	SOUTH DAKOTA
William C Chaney	TENNESSEE
Louis E Viko	UTAH
*C C Hillman	U S ARMY
*F L McDaniel	U S NAVY
*George Baehr	U S PUBLIC HEALTH SERVICE

Chairman Cocke at this point introduced President Roger I Lee .

DR ROGER I LEE Mr Chairman, members of the Board of Governors I have only a very short theme That theme is one I have had for some time concerning the functions of the Governors of this College I hope as the College grows, which it is doing, and as it acquires vitality, which it is doing, it will become more democratic and that the Governors will slowly acquire a great deal more influence in the affairs of the College Events in the College the last few years, particularly the development of its graduate courses and of its regional meetings, have indicated very clearly that the Governors are by process of evolution and by process of discussion acquiring more and more influence in the shaping of the policies of the College That is an excellent feature and as far as I have any influence, I shall support it That can be carried very much farther, very likely not all at once, but it is a healthy and wholesome growth . We want the College to be a democratic institution in a democratic country (Applause)

CHAIRMAN COCKE Gentlemen, we have lost one of our distinguished members by death, Dr LeRoy S Peters of Albuquerque, College Governor for New Mexico Proper notice was taken by your Chairman, who communicated with Mrs Peters, expressing our deep sympathy At this meeting a successor will be elected

We shall now hear the reading of the abstracted minutes of the last meetings of this Board at Boston in 1941

The Secretary read an abstract of the minutes of the two meetings in Boston in 1941 and these abstracts were approved as read

CHAIRMAN COCKE Are there any communications, Mr Secretary?

SECRETARY LOVELAND I have none

CHAIRMAN COCKE The next item on the agenda will be a report from the Executive Secretary, Mr Loveland

SECRETARY LOVELAND In line with our usual custom of keeping the Governors individually and as a whole advised and informed of happenings in the College, we have prepared for you, first, a list of all the candidates who have been acted upon by the Credentials Committee and the Board of Regents at the March and April meetings of this year Notifications were sent to all Governors of the elections that took place during December, 1941 The first group of names placed in your hands is that of candidates recommended for election by the Credentials Committee at a meeting on March 22, 1942, this list in the meantime having been approved by the Board of Regents The second list is a group which was recommended for election by the Credentials Committee on April 19, 1942, and which likewise has now been approved by the Board of Regents

I have also placed in your hands a sheet, entitled "Term of Associateship Expired" There are seven Associates who have failed to qualify for Fellowship in their maximum five-year term and under the By-Laws their names must now be dropped.

Since the last annual session of the College, we have lost by death 48 Fellows, 5 Associates—Total, 53 This is about the average loss by death annually in the last few years

Since the last session of the College, we have added 16 Life Members, making a grand total of 183, of whom 17 are now deceased, leaving 166

Additions by election include 137 Fellows and 100 Associates on December 15, 1941, and 165 Fellows and 121 Associates on April 19, 1942, or a grand total of 523 Most of the new Fellows have been advanced from Associateship There is a small shrinkage at the present time in the number of Associate candidates This will have some direct effect on the number of advancements to Fellowship in subsequent years The College membership is not materially increasing There are numerous losses by death, and the net increase in membership actually is about 150 to 175 per annum This is as intended by your Board of Regents, which has gauged the standards of admission accordingly

I have also placed in your hands, for your information, the financial statements of the College for 1941 These statements have been audited by a certified public accountant All details are given for those who are interested

CHAIRMAN COCKE Dr Edward L Bortz, Chairman, will now give the report of the Advisory Committee on Postgraduate Courses, the other members of this Committee being Drs James J Waring, Fred M Smith, Ernest H Falconer, and C Sidney Burwell

DR BORTZ Mr Chairman, Members of the Board of Governors After this Committee was appointed a year ago, it held a meeting and decided it would be advisable to offer approximately eleven postgraduate courses for the following year With that in mind, overtures were made to certain outstanding clinicians throughout the country and satisfactory courses were arranged With the national emergency that developed soon after December 7, 1941, the complexion of the postgraduate courses changed very radically and it was found expedient, because of the location of courses, or because of the involvement of large numbers of men who were on the faculties, or because of the lack of interest of members, to withdraw some of the courses Even so, with the six courses that were given—one in Boston, one in New York City, one in Philadelphia, one in Minneapolis, and two in Rochester, Minn—the total number of Fellows and Associates who took these courses equalled the number of registrants taking the courses a year earlier A year ago there were 228 this year, 226 Had all the courses been given this year and had there not been a national emergency, the number of registrants, we believe, would have been well over 300 In view of the adverse conditions which existed, we feel that this year's program was a notable success

We have talked with individuals who have been in attendance at all of the various courses this year and there have been not only commendation but expressions of approval in the most lavish terms, appreciation on the part of these student physicians for the high quality and intensive training that they have obtained through the College

It was my privilege during the last few days to be in Rochester and to listen to the course on cardiovascular diseases given by Dr E V Allen I want to say that in my mind it would be impossible to conceive of a course better balanced, more expertly executed by highly qualified teachers of national renown who constituted that faculty We must keep in mind that the College must accept its responsibility in carrying on the courses, and we do not know what the future has yet to offer, but we hope to carry on Thank you (Applause)

CHAIRMAN COCKE Thank you, Dr Bortz I know we all appreciate the excellent work of the Committee We have one of the Governors here who took one of the courses, and I am sure you would like to hear briefly from him Dr Lewis B Flinn of Wilmington, Delaware

DR FLINN Thank you, Mr. Chairman I attended the course in Rochester which Dr Bortz referred to, and I can do no more than to endorse all the remarks that he made about it I can think of no way that such a course could be improved upon, and I am sure that it was the unanimous opinion of all those fifty men who were there that the time spent was more than worth while

DR. ALLEN It would only be fitting to say that if our course was a success, it was due to the fact that we had a good deal of help from the outside About the time we had run out of ammunition, we were fortunate in having Dr Roy Scott from Cleveland, Dr Irvine Page from the University of Indiana, Dr Roger I Lee from Boston, and a number of others whom we were much pleased to have address us as guests They were just the element that gave the punch to make it seem to us like a reasonably satisfactory course

CHAIRMAN COCKE Gentlemen, I think we have a very fine showing of attendance by the Governors or their alternates Dr M C Pincoffs, Editor of the Annals, has told me that even though he is in military service his Assistant Editor, Dr Paul Clough, will carry on In spite of all of these terrible times, we should not relinquish any of our activities or interests in the College I think the feeling of the Board of Regents of the College is that activity should go on until such time as changes may become necessary

Is there any new business?

DR C W DOWDEN I should like to bring up a matter I have had on my mind for some time If you will look at your Program, you will find at the top of Page 5, "Qualified physicians who may wish to attend this Session as visitors, such physicians shall pay a registration fee of \$12 and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee"

In the neighboring city of Minneapolis, we have meetings known as "The Young Men's Clinical Association" or some such name, comprised of young men under the age of thirty-five, who will probably make a considerable portion of the future membership of this College Most of them are engaged in research work or in teaching I understand that they can visit this meeting only upon payment of a \$12 registration fee Most of them have access to the ANNALS One of our Louisville members has expressed himself as being opposed to this sort of thing Then, too, there are other physicians, surgeons, who would like to attend these meetings, and they also have access to the ANNALS These men say they often learn more at our meetings than they do at the surgical meetings and yet they must pay \$12 to register We have within one hundred miles a big clinic in which a relatively small percentage of the men are members of this College They, too, have access to the ANNALS and yet they must pay, I understand, a registration fee of \$12 I think that the College is too big for that It seems to me this is a subject that can be discussed and we might thereafter approve of some plan The main criticism is going to be the lack of facilities to take care of guests That would have to be worked out Certainly, in our general sessions, we can accommodate them In our hospitals and clinics some plan would have to be devised It does not seem quite right to me that this sort of thing should go on without something being done about it

CHAIRMAN COCKE There can be considerable clarification by the Executive Secretary, who will add some light to this before we open it for discussion

SECRETARY LOVELAND Dr Dowden is correct in one of his assumptions, that this rule was adopted at a time when our members became somewhat annoyed with non-members taking up the places at the clinics The present regulation was adopted by the Regents twelve years ago at our Minneapolis meeting. It was then pointed out that a great many physicians expressed the opinion that there was no need to join the College because they could take advantage of its meetings for nothing, whereas they would have to pay dues if they were members

There is one impression I should like to correct. Any member of the College, who communicates with my office and states that he has a close friend or an assistant working with him whom he would like to bring to the meeting, is sent a courtesy card with an invitation for that doctor to come as a guest. Dr. Allen of the Mayo Clinic can tell you that we issued formal invitations to all graduate students from that institution to come to this meeting as guests. This was also done in connection with the University of Minnesota and in connection with the members of the Ramsey County Medical Society and the Hennepin County Medical Society.

The reason the \$12 registration fee was selected was because the Associate dues in the College are \$12. At the time the rule was adopted the annual sessions were the chief activities of the College. The Regents felt that someone outside the College ought to be willing to pay as much as an Associate for the benefit of attendance. There is no desire on the part of the College to collect money from guest physicians; the object is to protect our membership, assuring them of accommodation at all features on the program. You probably do not realize the difficulty we often experience in providing accommodations for our members alone, not only at clinics and panel discussions, but even to secure hotel accommodations. At our St. Paul session we shall have no difficulty with the panel discussions because the rooms are large, but this is not always so or possible.

DR. DOWDEN: Mr. Loveland, isn't there some plan that might be worked out—a plan that would take care of just such problems as we have been discussing? Of course, I do not mean to throw our meetings open to the whole medical field.

SECRETARY LOVELAND: It is certainly worthy of consideration. Whatever can be done without reducing seriously the facilities to our members would be appropriate.

CHAIRMAN COCKE: Would anyone else like to speak?

DR. GRIFFITH: Mr. Chairman, I agree with Dr. Dowden in regard to the charge. If we are going to make a charge, and we charge Associates \$12 a year dues, we could open up our postgraduate courses to these registrants who want also to attend our annual meetings. In our meetings in Kansas City of the Southwest Clinical Society we charge those who wish to attend just half of what the regular fee for membership is. That holds down to a certain extent the number of attendants that would come if everything were free. We do, as Mr. Loveland said, have to protect our members. I do not think we should eliminate a registration fee, but it might be all right to reduce it.

CHAIRMAN COCKE: I will say for the benefit of certain of these postgraduate courses that have not been fully subscribed, that they have been filled in by non-members of the College under certain situations, so that it is a rather flexible arrangement, but the crux of the situation seems to concern whether the men should be allowed also to come to the annual sessions and pay a nominal registration fee rather than the present fee of \$12. The present arrangement was a self-protective measure that became necessary in the past.

DR. IRVING S. WRIGHT: Just to have it on the record, I attended the American Federation for Clinical Research and the President announced at that time that inasmuch as they would meet in different parts of the country, there was no fixed policy to meet at the time of the American College of Physicians session. Therefore, if this came up for special consideration, that might be borne in mind.

CHAIRMAN COCKE: Gentlemen, I would say that this situation was taken into consideration by the Board of Regents last year and it was understood that the Federation would not regularly meet in conjunction with the College. However, it has been brought out that the College would extend every courtesy to the members of that Federation when it held its meeting in proximity to that of the College. Mr. Loveland tells me that this year the courtesy of attending our meeting was extended to them.

DR RUSSELL To cover the ground, might we not revise the announcement in the Program, stating that the \$12 registration fee will be charged to qualified physicians "except those specifically invited " Let there be a clear understanding of the application of the registration fee and let it be known that any person who seems particularly desirable and whom a member wants to bring along, shall receive an invitation

CHAIRMAN COCKE That is, within the bounds of propriety

DR YATER I second that

CHAIRMAN COCKE We can trust to the diplomatic phraseology of our Executive Secretary to fix up the announcement as it should be Is there any other discussion? Are you ready for the question?

There was no further discussion The question was called and the motion carried

DR STRONG Mr Chairman, I should like to bring a matter to the attention of this Board I come from Vancouver, British Columbia, out on the edge of the continent A matter has come to my attention several times and was brought again to my attention today by a member from that area It is in regard to the notices of our meetings—for instance, the notices that carry with them the selection of clinics, panel discussions, etc , as well as the notices for the postgraduate courses These notices are sent from the headquarters in Philadelphia by ordinary mail They reach Vancouver in four or five days and obviously the notices mailed to members closer to Philadelphia have long since been delivered This places members at far-away points at a disadvantage in registering for postgraduate courses, for clinics or panels, and by the time their applications arrive the capacities are often exhausted In the interest of equity, would it not be possible to fix some scheme of zoning the country so that these notices may be delivered in a more equitable fashion? Even if our members in our location reply promptly, the applications will reach Philadelphia after many of the men from the more populous districts have replied The central office of the College naturally makes reservations as received

CHAIRMAN COCKE Dr Strong's remarks are quite in order, and we should like to hear from the Executive Secretary as to the possibility of correction, because certainly it is not the desire or the intention to make any distinction whatsoever and no one should be deprived by reason of geography of his choice of clinics

SECRETARY LOVELAND Dr Strong is essentially correct This condition did not hold this year in regard to clinics or panels at our St Paul meeting, but this was because our facilities are practically unlimited However, it might readily have occurred in regard to some of the postgraduate courses I think Dr Strong's request is reasonable and the situation can well be remedied I will say, however, that as a matter of practice, we have always released mailings to the West Coast before those to the points nearer to Philadelphia, but possibly we did not allow enough time between the two groups The central office will carefully gauge the time of mailings in the future

DR BORTZ Mr. Chairman, owing to the present national emergency, a situation has arisen that never confronted this body before I am asked to bring to the attention of the Board the problem of those Governors who are going into military service and who, therefore, will be away from their natural place of residence For instance, Dr Charles E Watts, Governor for Washington, is now on active duty in San Diego His term of office terminates this year, but in all likelihood the Committee on Nominations will again choose to nominate him for that important office There may be many others involved Now, should these men resign from their positions as Governors of their particular states or territories, or should the men confer with the Executive Committee, or with the Regents, or with the President, and have an Acting Governor appointed to act for them, or just what is the solution? I present this for discussion

CHAIRMAN COCKE I will say, Gentlemen, that the matter has been brought to my attention only in one instance, the case of Dr Drake, Governor for Maine. However, he stated his duties would not take him more than sixty miles from his home, and while he would have time to attend to his duties as Governor, he was willing to resign. I requested him, certainly until this meeting, that since he would not be out of touch either geographically or otherwise with his duties, to continue if he had available time to function as Governor. Dr Drake, will you speak for yourself?

DR DRAKE I have not been able to live in my own locality right along, but I have been there frequently and nothing, such as proposals of membership and other matters, has come up that I could not handle.

DR DOWDEN I have one other matter which I am sure Mr Loveland can clarify for me. We have in our section one young man who has just finished his Associateship. He is in the Army. He won't have time to get his case records ready to qualify. He is taking his examination in the American Board today. He wonders what his status will be in case he passes his examination or in case he does not have time to prepare his case histories.

CHAIRMAN COCKE The Regents are going to be very lenient in this situation—that is, when a man is in military service and deprived of opportunities to meet the requirements. You may tell him that some provision will be made. I don't know just exactly what it will be, but the Regents have discussed it.

DR CASON I would like to move that the Board of Governors go on record requesting that no change be made that would not otherwise be made in the status of men either in the service or contemplating entering the service, and wherever it is requested by the Governor, that an Acting Governor be appointed until his return to his state.

DR KERR I second the motion.

DR DOWDEN Could that be amended to include not only the Governors but men coming up for their final examination or advancement?

CHAIRMAN COCKE That should be a separate motion.

DR CASON Let's keep this straight.

SECRETARY LOVELAND There is a special consideration in the matter of an Acting Governor. If a Governor of the College is on active military duty where he cannot be reached by the men in his state, the situation naturally would shut off all candidates from that state. We have had this experience for the first time this year. We had a new Governor for Panama and the Canal Zone. He left the Canal Zone but did not resign, and in addition, we were unable to contact him a part of the time. His address was changed two or three times. We had two candidates from the Canal Zone, Associates who wanted to come up for Fellowship, and under the By-Laws they could not come up for consideration because there was no one available to endorse them. We must have the machinery for an Acting Governor or someone to endorse a candidate if the regular Governor is on active duty at considerable distance.

DR CASON This was my idea, and I am asking that an alternate or Acting Governor be appointed to do that.

SECRETARY LOVELAND Mr Chairman, the resolution authorizing the appointment of an alternate Governor applies only to alternates to attend the annual meetings of the College. That provision was made a few years ago, and the alternate has only that authority.

DR CASON Could we then, as part of this motion, put in that the Board of Regents be authorized or requested to adopt a resolution authorizing the alternates in this emergency to have the additional authority to endorse candidates and perform other duties ordinarily required of the regular Governor?

This alteration to the motion was agreeable to the seconder.

DR BORTZ Because of the important work that the Governors have to carry on, might it not be wise and resourceful to consider at least the advisability of having one or even two or three alternates to the Governor as an established policy? There are, for example, many delegates to the House of Delegates of the A M A and alternate delegates from the different sections of the country Also, in many states there are delegates from the state medical societies, and these delegates, I believe, also have alternates We have over 3,500 Fellows, and we would certainly have a sufficient number to have one or two alternates to the Governor in each state There are many possibilities arising, such as moving from one locality to another, death, or unforeseen situations which might leave a Governor's area without representation, and it would seem to me at this time very helpful if at least one alternate or possibly a first and second alternate to a Governor be appointed for all of the different Governors' areas

CHAIRMAN COCKE Your remarks have been very interesting and worth while, but we are confronted with the By-Laws, and the By-Laws are something the Regents cannot change It states here, Article IV, Section 1, Paragraph Five

"Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed The same alternate shall not be appointed for more than two consecutive years "

The Board of Regents has no authority to change the By-Laws except by the necessary legal method Any proposal has to lie on the table and be published some thirty days before the annual meeting

SECRETARY LOVELAND An amendment to the By-Laws of the College must be submitted in writing to the Board of Regents at least thirty days before any annual meeting of the Members of the College

DR SLOAN Is there not some machinery which operates in this society in this emergency? If a Governor dies, what happens?

CHAIRMAN COCKE The President may appoint a Governor until the next regular election

DR SLOAN Would that not cover this situation?

CHAIRMAN COCKE I think it could, through the cooperation of the Governor

DR SLOAN Is there a possibility of granting a leave of absence and appointing an Acting Governor?

CHAIRMAN COCKE I think the Executive Committee, which has power to function in any emergency, might do that

DR CASON Isn't that what you would be doing under my motion?

DR WARING There are several problems involved here In the first place, there is some confusion because of the use of the word "alternate" for the Governor In the second place, some provision must be made about the old Governor, the one who goes into service and is no longer able to function on account of non-residence in his territory. Are we going to ask this man to resign or will he voluntarily do so? Or will someone be appointed in his place until he does resign? Some action ought to be taken, perhaps by correspondence with the Executive Office or the Governor, pointing out to that man that if he does go into service and the affairs of the College can no longer be attended to by his office, that he kindly notify the Executive Office so that the Executive Committee may appoint another in his place I understand that the Executive Committee has the authority to appoint someone in his place, and it seems to me it might be left to the Executive Committee whether or not somebody should be appointed temporarily or permanently in his place

CHAIRMAN COCKE As I understand the By-Laws, the President has power of appointment only in case of resignation or death I think we could get around this by a slight change in phraseology, using some such word as "substitute" Governor Whether that would be any different from "alternate" I don't know Outside of suggesting to the Board of Regents, I don't think we can approach this matter with any finality The Regents will be guided largely by our suggestions

DR BURGESS Mr Chairman, I would like to suggest to Dr Cason that he use in his motion "Acting Governor "

DR ALLEN There have been so many good ideas that it seems too bad to be in too big a hurry While we ought to consider the national emergency, it seems more possible for the Chairman to appoint a small committee to give this thorough consideration with the ideas that have been expressed here However, there is a motion before the House

CHAIRMAN COCKE presented the motion and it was carried

DR KRAUSE Frequently I have heard the desire expressed for information as to the proceedings in our panel discussions I wonder if there are any facilities by which notes could be printed and distributed to members who are unable to attend The panels are so small so far as the number they accommodate is concerned, and so very interesting and worth while, that many members have asked if they can obtain proceedings thereof

CHAIRMAN COCKE At this meeting the panel accommodations are unusually adequate Have any been over-subscribed?

SECRETARY LOVELAND No

CHAIRMAN COCKE The smallest panel room this year accommodates 175 and the larger rooms are unlimited

DR KRAUSE But there are several panels going on simultaneously and a member can attend only one at a time

CHAIRMAN COCKE The only solution would be the employment of professional reporters, which would be a considerable expense How that expense could be apportioned would be difficult

SECRETARY LOVELAND The transcription and distribution of panel discussions have received very careful study in former years We investigated the cost of employing reporters and making transcripts and then mimeographing enough copies not only for those who attended the panels, but for anyone who desired copies We found that for a single Session this cost would amount to from \$2,500 to \$5,000

CHAIRMAN COCKE I agree with Dr Krause that proceedings of the panels would be desirable except for the cost I myself have had to attend so many meetings that I have been deprived of many valuable panels

CHAIRMAN COCKE then read several announcements and declared the meeting adjourned, at 6 20 p m

Attest (Signed) E R LOVELAND,
Secretary

MINUTES OF THE BOARD OF GOVERNORS

ST PAUL, MINN

April 22, 1942

The second meeting of the Board of Governors, in conjunction with the Twenty-sixth Annual Session of the American College of Physicians, convened in the Municipal Auditorium, St Paul, Minn, Wednesday, April 22, 1942, at 12 noon, Chairman Charles H Cocke presiding and Executive Secretary E R Loveland acting as Secretary, and with the following members or their alternates in attendance

Oliver C. Melson	ARKANSAS
Ernest H Falconer	NORTHERN CALIFORNIA
*Edgar Hull	LOUISIANA
Henry R Carstens	MICHIGAN
Edgar V Allen	MINNESOTA
*Graham Asher	MISSOURI
*Harry T French	NEW HAMPSHIRE
George H Lathrope	NEW JERSEY
Charles H Cocke	NORTH CAROLINA
*L H Fredericks	NORTH DAKOTA
Alexander M Burgess	RHODE ISLAND
*L E Madden	SOUTH CAROLINA
Paul K French	VERMONT
Walter B Martin	VIRGINIA
*E G Bannick	WASHINGTON
Albert H Hoge	WEST VIRGINIA
Charles F Moffatt	QUEBEC
*J H Watkins	ALABAMA
Fred G Holmes	ARIZONA
Lewis B Flinn	DELAWARE
Turner Z Cason	FLORIDA
Charles Henry Sprague	IDAHO
LeRoy H Sloan	NORTHERN ILLINOIS
C W Dowden	KENTUCKY
Eugene H Drake	MAINE
Louis Krause	MARYLAND
John G Archer	MISSISSIPPI
Ernest D Hitchcock	MONTANA
*Irving S Wright	EASTERN NEW YORK
A B Brower	OHIO
Homer P Rush	OREGON
M D Levy	TEXAS
Elmer L Sevringhaus	WISCONSIN
Ramon M Saurez	PUERTO RICO
George F Strong	ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN
Roy E Thomas	SOUTHERN CALIFORNIA
James J Waring	COLORADO
*J. S Nickum	CONNECTICUT
Wallace M Yater	DISTRICT OF COLUMBIA
Cecil M Jack	SOUTHERN ILLINOIS
Robert M. Moore	INDIANA

Harold H Jones	KANSAS
William B Breed	MASSACHUSETTS
Warren Thompson	NEBRASKA
Nelson G Russell, Sr	WESTERN NEW YORK
Leander A Riely	OKLAHOMA
*L D, Sargent	WESTERN PENNSYLVANIA
John L Calene	SOUTH DAKOTA
William C Chaney	TENNESSEE
Louis E Viko	UTAH
Warren S Lyman	ONTARIO
*C C Hillman	U S ARMY
*F L McDaniel	U S NAVY
*George Baehr	U S PUBLIC HEALTH SERVICE

CHAIRMAN COCKE I have the privilege of presenting the President-Elect, Dr Paullin

PRESIDENT-ELECT PAULLIN Members of the Board of Governors, it would not be possible for me at the present time, with conditions as they are, to assume the responsibilities that naturally would fall on my shoulders as the incoming President of this Organization unless I felt and knew that I had such a group of men qualified to help carry on the duties and responsibilities of this organization To you, it is a great responsibility, and I look forward with the greatest of pleasure to your cooperation and help in maintaining the high ideals and standards for which this College stands During the past year it has been my pleasure by mail to contact most of you in this arduous task which the College assumes in the responsibility of aiding the armed forces Through your help and that of others, it has been possible to provide this service for the Surgeons General of the Army and Navy For this we are very grateful, because this work is not only most valuable to them, but it has been of the greatest usefulness from the standpoint of helping the medical profession We have attempted, through your hearty cooperation, to keep square pegs out of round holes, and we have tried to make available for the personnel of the Army and Navy the qualifications of the physicians so that these doctors would give their greatest opportunity of service to this country in this extremely important time For your cooperation and for your help I am indeed most grateful and I know that I can continue to expect it in the year that is before us Thank you (Applause)

CHAIRMAN COCKE The Secretary will now read the abstract of minutes of our preceding meeting

Secretary Loveland read the abstract of minutes of the meeting of Monday, April 20, 1942

CHAIRMAN COCKE I shall now report from the Board of Regents the following resolutions

1 By resolution the Board of Regents on April 21 provided that all Fellows and Associates of the College on full-time active military service, whether in the regular or reserve Medical Corps, shall from January 1, 1942, have full remission of dues, it being provided that such members shall inform the Executive Offices of the College of the date upon entry into active service and also the date of retirement from active duty The resolution further provided that the initial fee for such men shall be reduced to \$10 00

2 By another resolution the Board of Regents provided that any member of the Board of Governors called to active military service, thereby being unable to perform his duties as Governor, may temporarily be relieved by an Acting Governor appointed by the Executive Committee, due consideration to be given to any nomination or nominations made by the Governor who can not serve

I might also add that at this meeting, upon the suggestion of Dr Ernest E Irons, Chairman of the American Board of Internal Medicine, it was proposed that fees for the Board examination may be reduced from \$50 00 to \$40 00 and that the Fellowship initiation fee in the College may be reduced from \$80 00 to \$65 00, these reductions to apply to elections after January 1, 1943 Therefore, what formerly cost men a total of \$130 00 for Fellowship in the College and certification by the Board will be reduced to \$105 00 I think the Regents have met your request in a very fine way Has anyone anything he would care to say about this matter? If not, we will proceed with reports

Are there any committees that have not previously reported that would like to make a report now? Unfortunately, Dr Bortz, Chairman of the Advisory Committee on Postgraduate Courses, has to attend a Panel Discussion and he may be delayed in getting here

There is the matter of the reappointment of the Advisory Committee on Postgraduate Courses I take great pleasure in reappointing the exact committee which has functioned so admirably this year, consisting of Dr Bortz, Chairman, Dr James J Waring, Dr Fred M Smith, Dr Ernest H Falconer, and Dr C Sidney Burwell

We are now ready for new business

DR MELSON Mr Chairman, members of the Board of Governors, it seems to be a law of nature that loss is balanced by gain As you know, our General Chairman is going to be elevated to the position of Vice President of this College and we are to lose a very valuable instructor and his happy presiding qualities I rise to move that a resolution from the Board of Governors be submitted to the Board of Regents that a gavel be presented to Chairman Cocke on behalf of the Board of Governors from the College

Vice Chairman Dowden assumed the chair

DR BREED I second Dr Melson's motion

Vice Chairman Dowden presented the motion, which was unanimously carried, whereupon Chairman Cocke resumed the chair (Applause)

CHAIRMAN COCKE Gentlemen, I really cannot tell you with what sincere appreciation I feel this distinguished honor During my years of association with you, and I have been on this Board twelve or thirteen years with a fair proportion of them as your Chairman, I have met not only with your constant courtesy and loyal cooperation, but also with your very faithful and interested attendance at the meetings This meeting is probably the largest, and to have such a gathering at such times as these is most gratifying I feel that the spirit of this Board of Governors is going to carry on and add more and more to the advancement of this College, which we think has such a worthwhile destiny I thank you deeply (Applause)

DR BROWER Mr Chairman, recognizing that we must lose you as Chairman, I suppose it is in good form to consider the incoming Chairman. I have in mind a man who has served on many important committees, he has always had the deepest interest of the College at heart, a man who last year helped to make the meeting in Boston probably one of the best we have ever had It gives me pleasure, Gentlemen, to nominate Dr William B Breed of Boston as Chairman of this Board of Governors for a term of three years

DR LATHROPE I second the nomination I have been a member of this Board only two or three years The pace that Dr Cocke has set as Chairman has been a pretty good one as has just been testified to You saw what a grand job was done by the gentleman from Massachusetts a year ago We all know his personality, and I know no one who would be better qualified or better able to keep up to the current that has already been set

CHAIRMAN COCKE Do I hear other nominations?

DR DOWDEN Mr Chairman, I move that nominations be closed and the Secretary cast the ballot for Dr Breed

Chairman Cocke called the question and the motion was unanimously carried, and the Secretary cast the ballot for Dr Breed's election

DR BREED Gentlemen, I appreciate the confidence you have placed in me by making me Chairman of this Board. I cannot predict what this Board will be like without Dr Cocke. He has been Chairman ever since I have been on the Board, and I do not see how anybody could keep the pace Dr Cocke has set.

CHAIRMAN COCKE There is another important office—not an office but a position to be filled, which is the function of this Board, and that is a membership on the Credentials Committee. Needless to say, this requires continuity of service and experience. Dr J O Manier's term expires at this meeting. He is eligible for reappointment if desired. I should like to hear suggestions as to whom the Board desires to appoint.

DR DOWDEN I move, Mr Chairman, that Dr Manier be reappointed.

DR LATHROPE I second the nomination.

CHAIRMAN COCKE Do I hear other nominations? All those in favor of Dr Dowden's motion will signify by saying aye, opposed, no.

The motion was unanimously carried.

CHAIRMAN COCKE That appointment is for three years. This Committee is constantly renewed or appointed and it has a fair degree of continuity. My own term of service on the Committee is not the problem of this Board but that of the Board of Regents. It expires this year.

SECRETARY LOVELAND The Board of Governors, however, must appoint another member on the Committee on Credentials to fill out the unexpired term of the Chairman, because Dr Cocke's retirement from the Board of Governors creates a vacancy. The Board of Governors appoints three members of this Committee as does also the Board of Regents. I feel sure the Board of Regents will want to retain Dr Cocke's services on the Credentials Committee, but if so, his appointment will be from among those selected by the Board of Regents.

DR RUSSELL I would like to nominate Dr Wallace M Yater.

DR DOWDEN I second the motion.

CHAIRMAN COCKE Do I hear other nominations?

There were no further nominations. The question was called and the motion was carried.

CHAIRMAN COCKE This appointment is for two years, until 1944.

Dr Nelson G Russell, Sr, Governor for Western New York, opened a discussion concerning the requirements for advancement to Fellowship insofar as certification by the American Board of Internal Medicine was concerned. It was clearly revealed that all Associates elected since April 6, 1940, shall present as one of the professional prerequisites for advancement to Fellowship certification by the American Board of Internal Medicine or by the certifying board in any of the allied specialties, with the exception that such certification shall not be required of candidates from the Army and Navy and Public Health Services, nor of candidates in whose specialty there exists no certifying board. Following this there was widespread discussion, in which various members of the Board of Governors joined, concerning qualifications for membership in the College and concerning the examinations conducted by the American Board of Internal Medicine. Out of this discussion there came certain suggestions concerning the type of examinations, both written and oral, which are now being given and the recommendation that an effort be made to encourage all applicants to take the examinations for entrance into the College, but that the Board of Regents of the College be requested to inquire into the present workings of the examining board and possibly to recommend that the type of examination should differ from the ordinary academic examination and be a more comprehensive test of the clinical knowledge of the applicants in handling patients, as well as contain some theoretical questions relating to problems which have very little or no clinical significance.

DR WARING Mr Chairman, I should like to bring up for discussion a matter relating to the interpretation of the essential work carried on by the industrial hygiene clinics by the induction of important members thereof into the military service At present the Army and Navy have directly under their supervision the manufacture of munitions for the war services, and in both of these organizations and in particular companies involved, the Army and Navy have deferred the doctors and the important assistants in their laboratories from induction into the armed forces At the present time members of the state boards of health are automatically members of the U S Public Health Service, as I understand it, and all of their laboratory assistants are deferred in order that the health of the people in the various states may be protected But, this protection has not extended, up to the present time, to the industrial hygiene clinics, heads of those clinics, and their laboratory assistants in industry This is a very important matter

In the Colorado University School of Medicine there is a Division of Industrial Hygiene and the man at the head of this has had a nation-wide opportunity to render *very important service to industry and the protection of employees of industry* against occupational diseases Under the pressure of the present emergency all of these industries are trying desperately to produce military supplies as rapidly as possible The methods that have been put into effect in manufacturing these munitions have not in every case succeeded in protecting many employees against occupational diseases such as lead poisoning, metallic poisoning, dust in the lungs, etc In Colorado this matter of dust in the lungs is extremely important The man who is head of our industrial division of hygiene has set up industrial clinics in various parts of the country In many of these clinics work has been disrupted by the removal of the doctor in charge In one important clinic the work was disrupted by the removal of the doctor and the technical assistant The same thing has applied to the Colorado Mining Company at Pueblo, the same to the industrial hygiene clinics in various subsidiary companies—The American Brake Shoe & Foundry Company and others At the present time the Army and Navy protects its own industrial hygiene plants The State Board of Health and the people are protected, and the people in industry are not protected

It is extremely difficult to replace these doctors who are removed from these industrial and hygiene clinics and it is much more difficult to replace their technical assistants, who are also being removed and taken into the service This same thing applies to many other occupations besides those immediately concerned in the medical profession It applies to chemistry I heard an important man talking over the radio from England recently He spoke of the tragedy of putting important manpower into the expeditionary forces He said he saw a man who had a national reputation as a chemist in America, serving in the forces That is only an isolated instance, but I could name for you half a dozen or more specific instances of the same sort

The American College of Physicians is going to have to recognize that situation and perhaps do what some other organizations have done The American Chemical Society has pointed out the flaws in the induction of men to service and has gone on record protesting against the inefficient way that induction is handled

I bring the matter up for discussion, Mr Chairman If you agree with me, I shall be glad to present a motion later

CHAIRMAN COCKE Let us have a little discussion We have with us one who is intimately acquainted with the situation—Dr Paullin

DR PAULLIN I do not want to monopolize the time of this Board, but I think I can help Dr Waring straighten out his problem very easily The Procurement and Assignment Agency is a Federal agency In each state of the Union there is appointed a chairman and in each co-area there is a co-area chairman On this Board there are two physicians in general practice, one physician from the American Asso-

ciation of Medical Colleges, one member from the American Veterinary Association, and two dentists This co-area committee and the state chairman work in cooperation with the Selective Service, Act Number 1 and Act Number 2

In medical work, one is permitted to write out a list of his essential teachers in a particular department—an essential list of individuals who are necessary in these industrial plants If these men are subject to Selective Service, they can be deferred by the local draft board after consultation with the state chairman or if they do not get satisfaction from the state chairman, they can appeal to the area committee, and if satisfaction is not obtained there, one can appeal to General Hershey There is ample machinery to protect all of these men in any vital industry All one has to do is to go to the state chairman and present his case—show the need and immediate advice will be sent to the local Selective Service Board, because this Board is required by Act of Congress to accept the recommendation of this Committee on Procurement and Assignment The machinery is all there, all you have to do is to use it

Of course, there is at present great difficulty in establishing standards for essential industry When you realize the extreme need in the Army at present, it is easier to understand things Furthermore, all of the needs of the country are paramount to every other thing The country's needs come first, civilian needs are next, and it is going to be a difficult problem to establish a yardstick by which you can determine the essential need of any given industry or teaching unit or Public Health Service

In so far as medical service is concerned, civilian needs, public health needs, and Army needs have got to be rationed and the greatest use made of the manpower that we have at our command The requisitioning agencies that are constantly sending in requests for doctors do not seem to realize that there are only 189,000 physicians in the United States I believe that the Office of Civilian Defense has full power to requisition the doctors they need I am quite certain from observation and experience with the service for the past two years that it is functioning just as well as it possibly can

DR WARING I am afraid Dr Paullin misunderstood me somewhat We are not concerned by interruption in the Medical School It is not the young men in the industrial hygiene clinics nor the technical assistants, it is the young men who are constantly trained in carrying out certain essential technical procedures in the laboratories of these industrial hygiene clinics Dr Paullin has a much more optimistic view of the way it functions than I have Mr Cummings, who is in charge of hygiene at our medical school, tells me that during the past six months he has been called a dozen or more times a day There is desperate need all over the country, and it is being constantly demanded that he furnish technical assistants who are being taken from the industrial hygiene clinics scattered over the country There is not at the present time in the Office of Production Management any specific responsible person or committee that has the specific responsibility of taking care of this situation It is looked after by the Army for the particular companies that are immediately under the management of the Army, it is taken care of by the Navy in the Navy Yard under the management of the Navy, it is being taken care of by the U S Public Health Service as far as the State Board of Health and all their technical assistants are concerned It is absolutely not being taken care of so far as it relates to the industrial hygiene clinics, and that is absolutely true in the case of our experience in Colorado, and it must be true in many other instances all over the country

CHAIRMAN COCKE Col Hillman, would you care to comment?

COL C C HILLMAN It would appear that Dr Waring's chief concern is not about doctors but civilian technicians As I see it, it would take it out of the Procurement and Assignment Bureau and put it into the Selective Service I think the channels of relief should be sought through your State Selective Service organization, and if this State Selective Service does not feel competent or does not deem it advisable to act, one would have recourse to the National Selective Service Head-

quarters under General Hershey This is just one of many similar examples Just as a citation of something that came up a little while ago—there was a question of the manufacture of artificial limbs The question concerned whether or not their technicians should be inducted They thought there were not very many of this kind of technicians and that we are certainly going to need more artificial limbs and that, therefore, these technicians should be deferred It came to the Surgeon General's office, up through Selective Service I think it was acted favorably upon

CHAIRMAN COCKE Capt McDaniel, would you care to comment?

CAPT F L MCDANIEL Mr Chairman and Gentlemen In the Navy the damage so far is not so bad We are not using selectees The Navy is a voluntary organization up to the present time and the District Commandant can either accept or reject the application for enrollment or enlistment or commission, so that we are not taken by force nor are we taking by force anyone from any private industry or from any vital spot Of course, it may later come to that and the Navy may take selectees for the continuance of the war In that case, I think we would handle it as Dr Paullin has suggested, through the local draft boards and appeal to the central headquarters in Washington

When I make my personal report to Admiral McIntire, I shall be glad to mention this to him, and I am sure that he is in a position to take it up at the proper places

DR WARING I should like to make it perfectly clear that this problem does not apply solely to the 8th Corps Area because these industrial hygiene clinics that are served are scattered over the country There are numerous Selective Service agencies that are concerned and not solely one agency

DR PAULLIN I thought Dr Waring was thinking of professional persons I am sure Selective Service can help you with your technicians if you present your problems to it.

CHAIRMAN COCKE The Chairman of the Advisory Committee on Postgraduate Courses has come in Dr Bortz, will you give us a report?

DR BORTZ Mr Chairman, I reported on the postgraduate courses given this year at the preceding meeting of the Board of Governors, and following that we had a Committee meeting at which the members present were very positive in their ideas that we should carry on the work A suggestion was made that we make plans for a course in general medicine in Boston, a course in allergy in New York, a course in general medicine in Philadelphia, a course in general medicine at the Mayo Clinic, and a course in internal medicine at the Continuation Center of the University of Minnesota, Minneapolis The details concerning these courses, the dates, duration, etc will have to be worked out in conjunction with the leaders of the courses I have talked with representatives such as Dr Robert Cooke of New York, men from Philadelphia, Dr Allen of the Mayo Clinic, and with Dr Watson at the University of Minnesota, and all have voiced deep interest and assured the College of their utmost cooperation in endeavoring to work out an adequate and satisfactory program for next year Probably two courses will be offered in the early part of February and the other three courses will be pre-meeting courses

There were no further matters to be brought before the Board whereupon the meeting was adjourned at 2 p m

Attest (Signed) E R LOVELAND,
Secretary

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A FURTHER REPORT ON THE TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE BY INTRAMUSCULAR INJECTIONS, SUBCUTANEOUS IMPLANTATION OF PELLETS, AND SUBLINGUAL ADMINISTRATION*

By FRANK L. ENGEL, M.D., CLARENCE COHN,† M.D., and LOUIS J. SOFFER, M.D., *New York, N. Y.*

SINCE the original reports by Levy-Simpson¹ and Thorn^{2,3,4} on the use of desoxycorticosterone acetate in the treatment of Addison's disease, many further reports have appeared confirming its value and pointing out its limitations and toxic effects resulting from overdosage^{5,6,7}. In 1939 an advance in therapy was made by Thorn and his co-workers^{8,9} who utilized the technique of Deanesly and Parkes¹⁰ and maintained adrenalectomized dogs and patients with Addison's disease in good condition by implantation of pellets of crystalline desoxycorticosterone acetate subcutaneously. By this method a slow and steady release of hormone, calculated at about 0.2 to 0.3 mg. a day per pellet, could be effected, the pellets being of such a size as to last about one year. Since then others have reported their experience with pellet implantation,^{11,12,13} and more recently Thorn has reviewed his experience with a large series of cases^{14,15}. In 1940 Anderson and co-workers¹⁶ reported the successful use of a preparation of desoxycorticosterone acetate dissolved in propylene glycol and administered sublingually. These results were later confirmed by Turnoff and Rowntree¹⁷.

The treatment of Addison's disease by the older methods was not attended by any serious effects from overdosage of cortical extract. It soon became apparent, however, that desoxycorticosterone acetate was an extremely potent hormone and, when injudiciously employed, hazardous. As with the old cortical extract it did not represent complete replacement therapy.

* Received for publication December 22, 1941.

From the Medical Services of The Mount Sinai Hospital, New York City.

The desoxycorticosterone acetate (Percorten) was generously supplied and manufactured by the Ciba Pharmaceutical Co., Summit, N. J.

† Eugene Meyer, Jr. Fellow.

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Alarming hypertension, excessive retention of salt and water with peripheral and pulmonary edema and cardiac failure were reported with increasing frequency and several patients died as a result of this^{5, 11, 12, 14, 15, 18} Overdosage was also noted to be associated with other manifestations which sometimes were difficult to distinguish from incipient adrenal insufficiency Among these may be mentioned anorexia, headache, and muscular weakness The Mayo Clinic group^{19, 20} pointed out the dangers of restriction of potassium in patients receiving desoxycorticosterone acetate, and, in fact, suggest that the administration of potassium may be of value in patients manifesting toxic symptoms Thorn¹⁴ described the occurrence of marked muscular weakness and transient paralysis in a patient receiving the synthetic hormone The serum potassium was very low, and relief was achieved by administering potassium A similar phenomenon was noted in dogs by Kuhlmann et al²¹

From the beginning it has been clear that desoxycorticosterone acetate has little effect on the disturbance in carbohydrate metabolism in Addison's disease, and in this respect does not represent complete replacement therapy^{1, 12, 14, 19, 22, 23} The danger of hypoglycemia and of possible sudden death from this during treatment with the synthetic hormone has been repeatedly pointed out That other functions of the adrenal cortex may not be possessed by desoxycorticosterone acetate is suggested by the work of Ingle²⁴ who showed that, although desoxycorticosterone acetate was the most potent life-maintaining factor in adrenalectomized rats, it did not exert as potent an effect on the muscle work capacity of the rats as some of the other crystalline factors

Thus, although therapy with desoxycorticosterone acetate represents a real advance in therapy, its incautious use may be associated with real dangers, and its effectiveness is limited by the fact that it does not represent complete replacement therapy

RESULTS

In a previous publication¹² we reported our experiences with desoxycorticosterone acetate in the treatment of five patients with Addison's disease Four of these patients received implantations of pellets The present report deals with further observations on these four patients, some of whom have now been treated with desoxycorticosterone acetate for over two and a half years In addition, four new patients have been added to the series In the whole series, three are females and five are males, and their ages vary from 21 to 57 years A tuberculous etiology is definite in three cases and probable in three others

CASE REPORTS

Case 1 D G, a 23-year-old woman, whose history has been given in detail before,¹² had 10 pellets of crystalline desoxycorticosterone acetate implanted subcutaneously on September 16, 1939 The average weight of each pellet was 128 mg

and the total dosage was calculated to yield approximately 3 mg per day, which is equivalent to about 5 mg a day when given intramuscularly. At this time she was receiving no supplementary salt by mouth. Two months after implantation of pellets the blood pressure had risen to 150 mm Hg systolic and 95 mm diastolic, and on slight exertion would rise to 180 mm systolic and 110 mm diastolic, which was associated with dyspnea and cardiac palpitation. Her weight was 122 pounds (55 kg) as compared to 104 pounds (47 kg) prior to therapy with desoxycorticosterone acetate. Blood electrolytes were entirely normal. For this reason she was readmitted to the hospital (November 10, 1939 to December 3, 1939) for restudy and for removal of pellets. A low salt diet yielding approximately 3 gm of sodium chloride a day had no effect on the blood pressure. On November 22 an area of fluctuation appeared at the lower end of the scar and two fragmented pellets were extruded. Following this, there was no appreciable change in blood pressure or weight. On December 3 a third pellet weighing 91.8 mg was removed. This represented a loss of 36 mg in weight of the pellets in the course of 77 days, or 0.46 mg a day. At this time the blood sodium was 133.1 milli-equivalents/L, the chloride 108 me/L, and the potassium 6.9 me/L. On December 11 the blood pressure was still 160 mm Hg systolic over 100 mm diastolic, so a fourth pellet, weighing 96.7 mg, was removed. This pellet had broken down at the rate of 0.35 mg per day. The site of implantation still showed an area of fluctuation and a small amount of serum could be extruded. One month later her blood pressure was still elevated and her blood electrolytes were normal. Despite the persistent hypertension, she now felt subjectively well. On January 30 a fifth pellet was extruded from the area of fluctuation. This pellet weighed 64.4 mg and represented a daily yield of 0.5 mg. Thereafter, her blood pressure fell to within normal limits, ranging between 105–125 mm Hg systolic and 75–85 mm diastolic, she felt extremely well and was able to resume her occupation as a book-keeper. One month later she developed an upper respiratory infection with elevation of temperature to 102.4° F, but showed no evidences of adrenal insufficiency. At this time she was advised to resume taking 5 gm of sodium chloride a day. Shortly thereafter her blood sodium was 137 me/L, chlorides 104 me/L.

On June 18, 1940, nine months after the original implantation, she returned to the hospital with the complaint of increasing anorexia and weakness of two weeks' duration. On admission her blood sodium was 133 me/L, chloride 105 me/L, and urea nitrogen 12 mg per cent. Her blood pressure was 95 mm Hg systolic and 54 mm diastolic and weight 125 pounds (57 kg). Two days after admission she felt much weaker and her blood pressure had fallen to 70 mm Hg systolic and 50 mm diastolic. Since she was now in obvious adrenal insufficiency, she was given intravenous saline in addition to 12 grams of sodium chloride by mouth. For two days she received 10 mg of desoxycorticosterone acetate intramuscularly, then 5 mg daily for a week, and then 2.5 mg daily thereafter until implantation of pellets. After a week, salt was reduced to 6 gm a day. On this regime her blood pressure rose to 110–120 mm Hg systolic and 70–90 mm diastolic, and weight to 130 pounds (59 kg). On July 1 five pellets of desoxycorticosterone acetate with an average weight of 12.4 mg were implanted subcutaneously. She was discharged two weeks later with a normal blood pressure and normal blood electrolytes. She weighed 128 pounds (58.2 kg) and was taking 5 gm of supplementary sodium chloride a day. During the subsequent few months her general condition remained excellent and she was able to indulge in full activity including working eight hours a day and partaking of moderate exercise, such as dancing. Hypoglycemic symptoms, of which she had previously occasionally complained, were avoided by taking frequent small feedings of carbohydrate when she indulged in more than usual exertion. Her blood pressure ranged between 135–150 mm Hg systolic and 85–95 mm diastolic, but she complained of no dyspnea, palpitation, or edema. On September 11, ten weeks after implantation

a pellet weighing 105 mg erupted spontaneously. This represented a breakdown rate of 0.26 mg. a day. The blood sodium at this time was 135.4 me/L and chloride 111.0 me/L. Blood pressure was 135 mm Hg systolic and 85 mm diastolic. Thereafter, her course was excellent and she led an entirely normal life. Her blood pressure ranged about 125 mm Hg systolic and 90 mm diastolic.

On June 16, 1941, eleven and a half months after implantation, she was readmitted to the hospital complaining of decreasing appetite and strength and dyspnea on exertion, of about three weeks' duration. On admission, her blood pressure was 104 mm Hg systolic and 70 mm diastolic, weight 124.5 pounds (56.6 kg), hematocrit 33 per cent, blood sodium 140.2 me/L, chloride 100 me/L, and urea nitrogen 13 mg per cent. After five days without supplementary salt or hormone, her weight fell to 121 pounds (55 kg), blood pressure to 96 mm Hg systolic and 60 mm diastolic and her hematocrit rose to 37.4 per cent, but there was no significant change in the blood electrolytes. Nevertheless, it was felt that there was sufficient evidence to suggest mild adrenal insufficiency due to exhaustion of the pellets. She was started on 6 grams of additional salt and 2 mg of desoxycorticosterone acetate intramuscularly daily. After four days the latter was increased to 2.5 mg a day for three days and then reduced to 2.0 mg for the next three days. On 10 days of this régime her blood pressure rose to 120 mm Hg systolic and 86 mm diastolic, weight to 130 pounds (59 kg), and the hematocrit fell to 29.2 per cent.

At this time she was started on a trial period of desoxycorticosterone acetate in propylene glycol by the sublingual route, receiving 2 mg a day, a dose of hormone which was quite adequate by the intramuscular route. On 10 days of this therapy her weight fell to 126 pounds (57.3 kg), her blood pressure to 102 mm Hg systolic and 72 mm diastolic and her hematocrit rose to 36 per cent. Subjectively she felt as well as ever during this period. At the end of this period, her blood sodium was 139.9 and chloride 106.0 me/L.

After being restabilized on 2.5 mg of the hormone intramuscularly daily, four pellets of the crystalline desoxycorticosterone acetate with average weight of 125 mg each were implanted on July 16, 1941. The blood pressure on the day of implantation was 132 mm Hg systolic and 85 mm diastolic. One month after implantation a single pellet erupted spontaneously. Her blood pressure was 150 mm Hg systolic and 100 mm diastolic, and subjectively she felt quite well.

Discussion The untoward effects of overdosage with too many pellets which occurred on the first implantation were avoided on subsequent implantations, and the response to this type of therapy has now been excellent. The patient has been able to return to an entirely normal mode of living. The trial period with the sublingual preparation demonstrated that dose for dose this mode of administration was not as effective as the intramuscular or the pellet method.

Case 2. S. R., a 21-year-old man, previously reported as case 2, had 10 pellets of desoxycorticosterone acetate implanted subcutaneously on June 19, 1939, after having been maintained on the intramuscular preparation (5 mg per day) for three weeks. The average weight of each pellet was 103 mg. Directly after operation he received intravenous saline for 24 hours in addition to 10 grams of salt per day. As a result of this he promptly developed headache, edema, moderate hypertension, dyspnea, a gallop rhythm. When the extra salt was reduced to 2 grams a day, these untoward manifestations disappeared and he was discharged feeling much improved. The blood electrolytes were entirely normal. Four months later, his condition was excellent and the extra salt was discontinued. His blood pressure ranged between

130–140 mm Hg systolic and 80–90 mm diastolic. He was able to return to work in a machine shop and as a delivery boy. Eight months after implantation his weight and blood pressure were maintained and his blood sodium was 140 me/L and chloride 111.6 me/L.

On May 6, 1940, eleven months after implantation, he returned to the hospital because of increasing fatigue and weakness for one month. His weight was 130 pounds (60 kg) as compared to 138 pounds (63 kg) on discharge. His blood pressure was 120 mm Hg systolic and 78 mm diastolic, hematocrit 39.5 per cent, blood sodium 140.6 me/L, chloride 105.6 me/L and urea nitrogen 7 mg per cent. Since there was not yet conclusive evidence of exhaustion of pellets, he was discharged after several days' observation, taking 10 grams of salt daily. Under observation for the next month on this régime, he had increasing symptoms of weakness and anorexia, and his weight and blood pressure continued to fall. He was readmitted to the hospital on June 24. His weight had fallen to 124 pounds (56.4 kg), his blood pressure to 110 mm Hg systolic and 60 mm diastolic, his hematocrit was 38 per cent, blood sodium 137.2 me/L, chloride 106 me/L, and urea nitrogen 8 mg per cent. All extra salt was now discontinued for 10 days, but there was no appreciable change in his weight, blood pressure, hematocrit, or blood electrolytes during this period. The blood sodium was 135.1 me/L. Subjectively, however, he felt definitely worse than he did while receiving the hormone. Despite the inability to demonstrate further changes characteristic of adrenal insufficiency without using more drastic methods, it was decided to implant a small number of pellets, since his clinical condition had definitely deteriorated. Accordingly, on July 7, 1940, four pellets, weighing approximately 125 mg each, were implanted. On the basis of previous observations it was calculated that these should yield a total of approximately 1.2 mg a day and should last about one year, assuming a breakdown rate of about 0.3 mg per day. He was discharged taking 5 gm of salt a day. His weight rose to 130 pounds (60 kg) and blood pressure to 132 mm Hg systolic and 84 mm diastolic.

During the subsequent 11 months of observation his condition remained very satisfactory. He worked irregularly, but otherwise led a relatively normal life. For a time he developed a distaste for salt, as compared with a craving for it prior to adequate therapy. His blood pressure ranged between 110–130 mm Hg systolic and 70–90 mm diastolic, his weight remained constant, as did his electrolytes.

On June 9, 1941, eleven months after implantation, he was again admitted to the hospital because of the slow and insidious development of weakness, loss of appetite, and loss of weight over a two month period. The physical examination was essentially as before, except that he now had a palpable liver. His weight was 120 pounds (54.6 kg), hematocrit 44.5 per cent, blood pressure 90 mm Hg systolic and 60 mm diastolic, blood sodium 141 me/L, chlorides 106 me/L, and urea nitrogen 18 mg per cent. There was now obvious clinical evidence of adrenal insufficiency, despite the normal blood electrolytes, and he was started on 2 mg of desoxycorticosterone acetate intramuscularly and 6 grams of salt daily. Ten days later his weight was 127 pounds (57.7 kg), hematocrit 37 per cent, blood pressure 130 mm Hg systolic and 80 mm diastolic, blood sodium 140.8 me/L, chloride 115.0 me/L, and urea nitrogen 8 mg per cent.

A trial with the sublingual preparation of desoxycorticosterone acetate in propylene glycol was now begun, 2 mg being administered daily for three days and 2 mg twice daily for three days, at which time the experiment had to be discontinued because of the development of a tooth infection. However, on this régime he lost seven pounds in weight (3.2 kg), his hematocrit rose from 37 per cent to 40 per cent, and his blood pressure fell to 110 mm Hg systolic and 70 mm diastolic.

At this time he developed a toothache, for which an extraction was performed under mandibular block. Because of this he was again given the intramuscular

a pellet weighing 105 mg erupted spontaneously. This represented a breakdown rate of 0.26 mg a day. The blood sodium at this time was 135.4 me/L and chloride 111.0 me/L. Blood pressure was 135 mm Hg systolic and 85 mm diastolic. Thereafter, her course was excellent and she led an entirely normal life. Her blood pressure ranged about 125 mm Hg systolic and 90 mm diastolic.

On June 16, 1941, eleven and a half months after implantation, she was readmitted to the hospital complaining of decreasing appetite and strength and dyspnea on exertion, of about three weeks' duration. On admission, her blood pressure was 104 mm Hg systolic and 70 mm diastolic, weight 124.5 pounds (56.6 kg), hematocrit 33 per cent, blood sodium 140.2 me/L, chloride 100 me/L, and urea nitrogen 13 mg per cent. After five days without supplementary salt or hormone, her weight fell to 121 pounds (55 kg), blood pressure to 96 mm Hg systolic and 60 mm diastolic and her hematocrit rose to 37.4 per cent, but there was no significant change in the blood electrolytes. Nevertheless, it was felt that there was sufficient evidence to suggest mild adrenal insufficiency due to exhaustion of the pellets. She was started on 6 grams of additional salt and 2 mg of desoxycorticosterone acetate intramuscularly daily. After four days the latter was increased to 2.5 mg a day for three days and then reduced to 2.0 mg for the next three days. On 10 days of this régime her blood pressure rose to 120 mm Hg systolic and 86 mm diastolic, weight to 130 pounds (59 kg), and the hematocrit fell to 29.2 per cent.

At this time she was started on a trial period of desoxycorticosterone acetate in propylene glycol by the sublingual route, receiving 2 mg a day, a dose of hormone which was quite adequate by the intramuscular route. On 10 days of this therapy her weight fell to 126 pounds (57.3 kg), her blood pressure to 102 mm Hg systolic and 72 mm diastolic and her hematocrit rose to 36 per cent. Subjectively she felt as well as ever during this period. At the end of this period, her blood sodium was 139.9 and chloride 106.0 me/L.

After being restabilized on 2.5 mg of the hormone intramuscularly daily, four pellets of the crystalline desoxycorticosterone acetate with average weight of 125 mg each were implanted on July 16, 1941. The blood pressure on the day of implantation was 132 mm Hg systolic and 85 mm diastolic. One month after implantation a single pellet erupted spontaneously. Her blood pressure was 150 mm Hg systolic and 100 mm diastolic, and subjectively she felt quite well.

Discussion The untoward effects of overdosage with too many pellets which occurred on the first implantation were avoided on subsequent implantations, and the response to this type of therapy has now been excellent. The patient has been able to return to an entirely normal mode of living. The trial period with the sublingual preparation demonstrated that dose for dose this mode of administration was not as effective as the intramuscular or the pellet method.

Case 2. S. R., a 21-year-old man, previously reported as case 2, had 10 pellets of desoxycorticosterone acetate implanted subcutaneously on June 19, 1939, after having been maintained on the intramuscular preparation (5 mg per day) for three weeks. The average weight of each pellet was 103 mg. Directly after operation he received intravenous saline for 24 hours in addition to 10 grams of salt per day. As a result of this he promptly developed headache, edema, moderate hypertension, dyspnea, a gallop rhythm. When the extra salt was reduced to 2 grams a day, these untoward manifestations disappeared and he was discharged feeling much improved. The blood electrolytes were entirely normal. Four months later, his condition was excellent and the extra salt was discontinued. His blood pressure ranged between

130–140 mm Hg systolic and 80–90 mm diastolic. He was able to return to work in a machine shop and as a delivery boy. Eight months after implantation his weight and blood pressure were maintained and his blood sodium was 140 me/L and chloride 111.6 me/L.

On May 6, 1940, eleven months after implantation, he returned to the hospital because of increasing fatigue and weakness for one month. His weight was 130 pounds (60 kg) as compared to 138 pounds (63 kg) on discharge. His blood pressure was 120 mm Hg systolic and 78 mm diastolic, hematocrit 39.5 per cent, blood sodium 140.6 me/L, chloride 105.6 me/L and urea nitrogen 7 mg per cent. Since there was not yet conclusive evidence of exhaustion of pellets, he was discharged after several days' observation, taking 10 grams of salt daily. Under observation for the next month on this régime, he had increasing symptoms of weakness and anorexia, and his weight and blood pressure continued to fall. He was readmitted to the hospital on June 24. His weight had fallen to 124 pounds (56.4 kg), his blood pressure to 110 mm Hg systolic and 60 mm diastolic, his hematocrit was 38 per cent, blood sodium 137.2 me/L, chloride 106 me/L, and urea nitrogen 8 mg per cent. All extra salt was now discontinued for 10 days, but there was no appreciable change in his weight, blood pressure, hematocrit, or blood electrolytes during this period. The blood sodium was 135.1 me/L. Subjectively, however, he felt definitely worse than he did while receiving the hormone. Despite the inability to demonstrate further changes characteristic of adrenal insufficiency without using more drastic methods, it was decided to implant a small number of pellets, since his clinical condition had definitely deteriorated. Accordingly, on July 7, 1940, four pellets, weighing approximately 125 mg each, were implanted. On the basis of previous observations it was calculated that these should yield a total of approximately 1.2 mg a day and should last about one year, assuming a breakdown rate of about 0.3 mg per day. He was discharged taking 5 gm of salt a day. His weight rose to 130 pounds (60 kg) and blood pressure to 132 mm Hg systolic and 84 mm diastolic.

During the subsequent 11 months of observation his condition remained very satisfactory. He worked irregularly, but otherwise led a relatively normal life. For a time he developed a distaste for salt, as compared with a craving for it prior to adequate therapy. His blood pressure ranged between 110–130 mm Hg systolic and 70–90 mm diastolic, his weight remained constant, as did his electrolytes.

On June 9, 1941, eleven months after implantation, he was again admitted to the hospital because of the slow and insidious development of weakness, loss of appetite, and loss of weight over a two month period. The physical examination was essentially as before, except that he now had a palpable liver. His weight was 120 pounds (54.6 kg), hematocrit 44.5 per cent, blood pressure 90 mm Hg systolic and 60 mm diastolic, blood sodium 141 me/L, chlorides 106 me/L, and urea nitrogen 18 mg per cent. There was now obvious clinical evidence of adrenal insufficiency, despite the normal blood electrolytes, and he was started on 2 mg of desoxycorticosterone acetate intramuscularly and 6 grams of salt daily. Ten days later his weight was 127 pounds (57.7 kg), hematocrit 37 per cent, blood pressure 130 mm Hg systolic and 80 mm diastolic, blood sodium 140.8 me/L, chloride 115.0 me/L, and urea nitrogen 8 mg per cent.

A trial with the sublingual preparation of desoxycorticosterone acetate in propylene glycol was now begun, 2 mg being administered daily for three days and 2 mg twice daily for three days, at which time the experiment had to be discontinued because of the development of a tooth infection. However, on this régime he lost seven pounds in weight (3.2 kg), his hematocrit rose from 37 per cent to 40 per cent, and his blood pressure fell to 110 mm Hg systolic and 70 mm diastolic.

At this time he developed a toothache, for which an extraction was performed under mandibular block. Because of this he was again given the intramuscular

preparation of hormone, receiving 2 mg. a day. Three days later, trismus and some swelling in the submaxillary region were noted. Five days after the extraction his temperature suddenly rose to 103° F, and an intense brawny tender swelling developed on the entire left side of the neck, together with increased trismus, dysphagia, and glottal edema. Intravenous glucose in normal saline was administered, and the dose of desoxycorticosterone acetate was increased to 5 mg a day, and then to 5 mg twice a day during the acute illness. Frequent blood pressure determinations were made, and the hematocrit was determined daily. Since nothing could be taken by mouth, glucose in saline was administered intravenously continuously. On the second day his temperature had risen to 105.4° F, he responded poorly and was desperately ill. Chemotherapy with sulfathiazole intravenously was begun, but had to be discontinued on the fourth day because of the development of purpura due to thrombocytopenia. Fortunately, at this time improvement began to set in. During the acute febrile phase of the illness, which lasted six days, the hematocrit fell from 40 per cent to 30 per cent, the blood pressure ranged between 116 mm Hg systolic and 90 mm diastolic and 150 mm systolic and 85 mm diastolic, his weight rose from 118 to 120 pounds (53.7 to 54.6 kg), the blood sodium was 144.4 me/L, the chloride 115.0 me/L, and urea nitrogen 8 mg per cent during the height of the illness. At no time was more than 10 mg of desoxycorticosterone acetate given, and the salt intake varied between 10 and 19 grams a day.

Following this acute illness there was a definite increase in the patient's requirement for hormone as compared with the period prior to it. On 3 mg a day and 6 grams of salt he lost three pounds in weight and his hematocrit rose to 35 per cent during the first week after the acute illness, but thereafter he slowly regained weight and strength and his blood pressure averaged about 130 mm Hg systolic and 85 mm diastolic. He was discharged on July 27 with normal electrolytes, and weighing 122 pounds (55.5 kg), after having been taught to administer the hormone himself. He was readmitted on August 18. His weight was 125 pounds (56.9 kg), and the blood pressure was 132 mm Hg systolic and 90 mm diastolic. His general condition was definitely improved. He was then maintained on 2.5 mg and 6 grams of salt daily until implantation of four pellets, with an average weight of 125 mg, was performed on August 25. During the subsequent month of observation, his condition remained satisfactory.

It is interesting to note that this patient, who was the first to be implanted at this hospital and who originally received more pellets than he required, as was apparent from subsequent observations, did not develop serious toxic manifestations. Except for the brief period postoperatively, when he received an excessive amount of saline intravenously and developed transient hypertension and edema, he was very well during the first year.

No definite conclusions can be drawn concerning the value of the sublingual preparation in this case because of the complicating severe infection. In the management of the patient during this serious complication it should be emphasized that a relatively small amount of desoxycorticosterone acetate, 5 to 10 mg a day, was necessary to prevent the development of crisis, and that by careful check on the salt balance, edema and hypertension were avoided. The increased requirement for hormone after a severe infection has been frequently noted before.

Case 3. J. S., a 47-year-old man, previously reported as case 3, had 13 pellets of desoxycorticosterone acetate implanted subcutaneously on July 31, 1939, two

months after he came under our observation. For one month prior to implantation, he had been receiving 5 mg of the synthetic hormone intramuscularly and 10 grams of salt by mouth daily. Although on this régime the blood sodium and chloride, blood pressure and weight had increased, and the hematocrit and blood potassium had decreased, his clinical improvement had not been proportionately as striking and he continued to complain of weakness and anorexia. After implantation of pellets his strength and appetite improved slightly, but he now began to complain of precordial pain on slight exertion which was typically anginal in character and was relieved by nitroglycerin. His blood pressure was found to range between 150–185 mm Hg systolic and 80–98 mm diastolic. Since these symptoms were not relieved by discontinuing extra salt by mouth, four pellets were removed surgically on September 26. One month later the patient's blood pressure was 145 mm Hg systolic and 88 mm diastolic and his weight 121 pounds (55 kg), but he continued to complain of angina which incapacitated him as much as his Addison's disease had previously done. During the following three and a half months there was no appreciable change in his clinical status, and his blood pressure was found to be approximately 160 mm Hg systolic and 100 mm diastolic. He was readmitted to the hospital on January 15, 1940. During the month prior to admission he had lost 10 pounds in weight and his appetite had been poor. His blood pressure was 160 mm Hg systolic and 94 mm diastolic, hematocrit 44 per cent, blood chlorides 106 me/L, sodium 145 me/L, urea nitrogen 20 mg per cent, and sugar 55 mg per cent. The venous pressure and circulation time were normal and there were no clinical evidences of cardiac failure. The electrocardiogram showed no abnormality. Fundal examination revealed incipient retinal arteriolar sclerosis. Another glucose tolerance test again showed a flat curve. Under observation he had several episodes of precordial pain uninfluenced by placebos but relieved by nitroglycerin. On January 24, four pellets were removed surgically, leaving five pellets in situ. The pellets showed an average breakdown rate of 0.28 mg per day.

Despite the removal of the pellets observation during the next four months showed no improvement in his clinical condition. The hypertension and angina persisted, and the blood electrolytes remained normal in the face of poor appetite and strength and slow loss of weight. On April 30 he was again admitted to the hospital because of increasingly frequent attacks of sweating, coldness of the extremities, dizziness, and faintness, usually associated with a feeling of hunger and relieved by fruit juice. A glucose tolerance test showed a low flat curve, at the conclusion of which he had typical hypoglycemic symptoms, promptly relieved by orange juice. An electroencephalogram taken while fasting showed diffuse delta activity, uninfluenced by the administration of glucose. Because of previous observations on the inefficacy of the synthetic desoxycorticosterone acetate on the disturbance in carbohydrate metabolism¹² he was started on Upjohn's adrenal cortical extract, which was administered in a dose of 1 cc twice a day for 16 days. At the end of this period there was a slight but definite improvement in the appearance of the glucose tolerance curve, which returned to its original state one week after discontinuing the cortin. However, spontaneous hypoglycemic attacks occurred much less frequently.

In June, 1940, approximately 11 months after the implantation of pellets, his precordial pain began to diminish somewhat, his blood pressure decreased to 110 mm Hg systolic and 70 mm diastolic, and for several days prior to admission on June 12 he had noted nausea and diarrhea. The blood sodium was 135 me/L and chlorides 101 me/L. Since the patient showed obvious signs of exhaustion of his pellets, he was given an intravenous infusion of saline, following which he felt much better, and then was started on 8 grams of sodium chloride daily without the use of hormone. His blood pressure was maintained at 120–162 mm Hg systolic and 70–100 mm diastolic, and two weeks later his blood sodium was 140.2 me/L and chlorides 106

saline for 24 hours, following which there was marked symptomatic improvement, and his blood pressure rose to 100 mm Hg systolic and 68 mm diastolic. For one week he received salt alone, taking 12 grams a day. Although the blood chlorides rose to 615 mg per cent, there were no other appreciable changes. On July 29 daily treatment with 25 mg of desoxycorticosterone acetate intramuscularly and 8 grams of salt was begun. After 10 days his hematocrit had fallen to 35 per cent and his weight had increased from 141.5 pounds (63.8 kg) to 146.5 pounds (66.6 kg), but his blood pressure remained low, 98 mm Hg systolic and 70 mm diastolic, and he still felt quite weak and anorexic. The dose of hormone was, therefore, increased to 5 mg a day. After three weeks of this therapy his weight had increased to 150 pounds (68 kg) and his blood pressure had increased to 110 mm Hg systolic and 70 mm diastolic. He was taught to administer the hormone himself and was discharged to be observed for several months prior to implantation of pellets.

Two weeks after discharge he was feeling very well. His blood pressure was 130 mm Hg systolic and 90 mm diastolic, his blood sodium 138 me/L, chlorides 104 me/L, and his weight was unchanged. Salt was reduced to 6 gm a day. One week later his blood pressure was 142 mm Hg systolic and 100 mm diastolic, and the daily dose of hormone was reduced to 3 mg a day. He was now able to return to his occupation of cab driver. On October 3 his blood pressure was 130 mm Hg systolic and 90 mm diastolic, and the hormone was cut to 2 mg a day. A week later, the dose was reduced to 1.3 mg and on October 21 to 1 mg a day. At this time his weight was 152 pounds (69.2 kg), his blood pressure 142 mm Hg systolic and 90 mm diastolic, blood sodium 144 me/L and chlorides 109 me/L. On this dose for five days he lost three pounds in weight and his blood pressure fell to 105 mm Hg systolic and 75 mm diastolic. It was, therefore, felt that his requirement was more than 1 mg daily, and on October 30, four pellets of desoxycorticosterone acetate, with an average weight of 127 mg, were implanted. This was intended to yield about 12 mg of hormone per day. During the subsequent 10 months of observation he has done extremely well, indulging in full activity as a cab driver. His blood pressure is 130 mm Hg systolic and 80 mm diastolic and his weight 154 pounds (70 kg). The blood electrolytes have remained normal and, as yet, he has shown no evidence of exhaustion of the pellets.

This case demonstrates the value of prolonged and careful observation of the response to the intramuscular preparation and the determination of the smallest possible dose which will maintain the patient, before implantation is performed. In previously untreated patients the hormonal requirement will very definitely decrease during the first few months of successful therapy. Failure to take this into account is responsible for the appearance of overdosage manifestations.

Case 7 J K, a 46-year-old delicatessen clerk, who complained of fullness after eating and occasional nausea of three years' duration, was first admitted on August 16, 1940. Roentgen-ray studies eight months previously were said to show a duodenal ulcer. Five weeks before admission, he gradually lost his appetite, became weak, and had nausea after eating. He lost nine pounds and noted that his skin was becoming darker. For one week he had dyspnea on exertion and dizziness on arising from his bed in the morning. He has noted a definite craving for salty foods.

Physical examination revealed a thin, well developed man, with deep pigmentation of the skin and several bluish-brown pigmented areas on the buccal mucosa and hard palate. The heart and lungs were clear. The blood pressure was 80 mm Hg systolic and 60 mm diastolic while reclining, it fell to 70 mm systolic and 60 mm diastolic.

after standing, and was associated with dizziness. The lower pole of the right kidney was palpable. The superficial reflexes were absent.

On admission on August 16, 1940, the patient weighed 131 pounds (59.5 kg). His blood pressure was 86 mm Hg systolic and 60 mm diastolic, and the hematocrit was 41 per cent. The blood urea nitrogen was 24 mg per cent, and a glucose tolerance curve showed a maximum use of the blood sugar to 120 mg per cent. Unfortunately, because of technical difficulties, the blood electrolyte studies could not be done at this time. He was started on 12 grams of added salt a day and after two weeks of this regime he showed considerable symptomatic and objective improvement. His weight rose to 142 pounds (64.5 kg), his blood pressure to 110 mm Hg systolic and 70 mm diastolic, and his hematocrit fell to 37 per cent. The postural hypotension disappeared. The blood sodium at this time was 133.5 me/L and chlorides 102.0 me/L, urea nitrogen 9 mg per cent. The added salt was now stopped for one week, at the end of which time he felt definitely weaker, although his blood pressure did not show any change. He lost two pounds in weight, and his hematocrit rose to 42 per cent. The blood sodium was 136.6 me/L and chlorides 102 me/L. From September 11 to 17 he received 5 mg of desoxycorticosterone acetate intramuscularly and 8 grams of salt daily. On this he gained 10 pounds in weight and his hematocrit fell to 34 per cent, whereas his blood pressure rose to 145 mm Hg systolic and 90 mm diastolic. Hormone and salt were then again stopped for 10 days, during which time there was a progressive loss of weight to 140 pounds (63.6 kg), a fall in blood pressure to 110 mm Hg systolic and 70 mm diastolic, and a rise in hematocrit to 40 per cent, associated, however, with only a slight decrease in the feeling of well-being. Sodium chloride balance studies at this time demonstrated that on an intake of approximately 5 gm of salt (ward diet) a day he was excreting 15.16 grams of NaCl. For 48 hours his salt intake was cut to less than 0.5 gram a day, and on this he excreted 7.75 grams and 4.06 grams of sodium chloride per day. This remarkable negative salt balance was reflected in the blood sodium and chloride values which were 127.3 me/L and 96.0 me/L respectively. His weight decreased and his hematocrit rose to 44.5 per cent during the 48 hour period. His blood pressure was sustained until the very end of the period, when, on getting out of bed, he suddenly felt very weak and faint and at that time his blood pressure was 88 mm Hg systolic and 55 mm diastolic. Intravenous saline, salt by mouth, and 5 mg of synthetic hormone were administered and he made a prompt recovery. On three days of treatment with 5 mg of hormone and 6-12 grams of salt a day, he gained 10 pounds (4.5 kg), his hematocrit fell to 32.5 per cent, and his blood pressure rose to 140 mm Hg systolic and 90 mm diastolic. These studies having established the diagnosis of Addison's disease beyond any doubt, the period of stabilization and assay of hormone requirement was begun. He was discharged on October 13, taking 2 mg of hormone administered by himself and 6 grams of salt daily.

One month later he was feeling very well, but his blood pressure had reached 150 mm Hg systolic and 98 mm diastolic. The hormone was, therefore, reduced to 1.5 mg daily and a few days later to 1.0 mg, and the salt to 3 grams a day, since the blood pressure remained elevated. His weight was 150 pounds (68.2 kg), and there was no edema or evidence of cardiac failure, although he did occasionally complain of palpitation. A palpable liver was noted for the first time, and it has remained palpable ever since. On December 3, almost two months after discharge, he was readmitted for pellet implantation. His weight was 151 pounds (69.7 kg), his blood pressure 145 mm Hg systolic and 85 mm diastolic, and hematocrit 34 per cent. It was felt that his requirement was less than 1 mg a day, and on December 8 two more pellets, with an average weight of 25 mg, were implanted and were calculated to be roughly approximately 0.6 mg of hormone a day for about one year. Following implantation his blood pressure showed a gradual downward trend to 110 mm Hg systolic.

mm diastolic to 135 mm systolic and 80 mm diastolic, and his hematocrit rose to as high as 42 per cent despite increasing the salt intake to 10 to 12 grams a day. Nevertheless, he felt extremely well and his weight increased to 159 pounds (72.3 kg). However, in view of this apparently large requirement of salt which seemed necessary to keep him in good condition, it was decided to implant one more pellet and reduce the salt intake to 6 gm a day. Accordingly, this was done on December 24.

Within two weeks of the implantation, the patient returned weighing 163 pounds (74.1 kg), with edema of the face and legs, and with a blood pressure of 150 mm Hg systolic and 90 mm diastolic. His appetite and strength had decreased and he complained of headache. Added salt was discontinued and he was advised to avoid salty foods. Two weeks later there was no change. His blood sodium and chlorides at this time were 145.7 me/L and 101 me/L respectively. Potassium chloride in a dose of 3 grams a day was administered for two weeks without effect. He was, therefore, readmitted to the hospital for removal of a pellet. On admission, his weight was 160 pounds (72.8 kg), blood pressure 140 mm Hg systolic and 100 mm diastolic, hematocrit 41 per cent, blood sodium 141.5 me/L and chlorides 100 me/L. On March 3, one month after removal of the pellet, there was still no change in the edema. The patient's weight was 164 pounds (74.5 kg), and his blood pressure 140 mm Hg systolic and 90 mm diastolic. Thereafter, however, there was a gradual spontaneous disappearance of the edema, loss of weight to 153 pounds (69.5 kg), and fall in blood pressure to 130 mm Hg systolic and 80 mm diastolic. Strength, appetite, and general feeling of well-being improved sufficiently to enable him to return to his occupation as a delicatessen clerk. During the summer he took 2 grams of added salt a day. At present, 10½ months after implantation, he is beginning to show symptoms which may herald the exhaustion of his pellets.

This case demonstrates the marked sensitivity of some of these patients to relatively small variations in salt and hormone intake. A gain or loss of 10 pounds in weight and 10 per cent in the hematocrit in a short time was not unusual. It is interesting to note that, with the exception of the salt deprivation test, the blood electrolytes were never low enough to be diagnostic. The marked variations in weight, hematocrit, and blood pressure, and the disappearance of postural hypotension after salt administration alone were sufficient to establish the diagnosis. The caution which must be observed with the salt deprivation test is again demonstrated here. The occurrence of edema and hypertension after the addition of one pellet yielding approximately 0.3 mg a day, its failure to subside after limitation of sodium chloride intake and administration of potassium, and its persistence for approximately a month after the removal of this pellet, are interesting.

Case 8 H J, a 36-year-old German refugee with a family history of tuberculosis, was first admitted on December 10, 1940. For the past year she had been living with a relative who had open tuberculosis. She had always been dark-skinned, but had noted increasing pigmentation of the skin and mucous membranes during the past two years, and especially during the past few months. One and a half years previously she had had a low-grade fever, and eight months before admission developed fever and pain in the left chest. Seven weeks before admission she had had a low fever again and had noted generalized malaise and marked weakness. Occasionally during the past few weeks she had vomited. Physical examination revealed a well developed female with marked pigmentation of the skin and mucous membranes. The tongue showed linear gray pigmentation in

ings near the circumference. There was marked grayish-brown pigmentation of the gums and lips and a few pigment patches on the buccal mucous membranes. The skin showed diffuse brown pigmentation, slightly darker on the face, and with a distinct exaggeration in the perineum, axillary folds, areolae of nipples and dorsum of the knuckles. The creases of the palms were brown, and there were several inky black freckles on the face and arms. The heart and lungs showed no abnormal physical signs. The blood pressure was 105 mm Hg systolic and 80 mm diastolic. The blood urea nitrogen was 16 mg per cent, the serum sodium was 129.1 me/L, the chlorides were 96 me/L, and the potassium was 5.3 me/L. The glucose tolerance test revealed a flat curve with a maximum rise of the blood sugar to 105 mg per cent.

On admission the patient was considered to be a typical case of Addison's disease in moderate adrenal insufficiency. For this reason she was started on a continuous intravenous infusion of normal saline. In addition, she received 12 grams of sodium chloride by mouth and 10 mg of desoxycorticosterone acetate intramuscularly daily. At the onset of therapy the blood pressure was 92 mm Hg systolic and 65 mm diastolic. After receiving 2100 cc of saline intravenously, in addition to the salt by mouth, in the course of 48 hours, she improved considerably and the intravenous saline was discontinued. During the next few days the intake of salt was cut to 2 to 6 grams a day, depending on her clinical appearance from day to day. Desoxycorticosterone was reduced to 5 mg per day. The blood pressure rose to 102 mm Hg systolic and 64 mm diastolic. The hematocrit was 31 per cent. At this time the patient began to show mental symptoms. She was alternately euphoric and depressed. She continued to take fluids by mouth and imbibed large quantities of fruit juices. Because of the psychotic state and the vomiting, 5 per cent glucose in saline was administered. On the possibility that the psychosis may be in some way related to disturbed carbohydrate metabolism in the central nervous system, and since the desoxycorticosterone acetate is known to have no appreciable effect on carbohydrate metabolism, the latter was discontinued and Upjohn cortical extract, in doses of 5 to 10 cc daily, was administered. At no time during this period was a low blood sugar found. It was eventually felt that the psychotic episode represented an exhaustive psychosis. After three days the mental state improved. Because of a slight rise in hematocrit and fall in blood pressure, the desoxycorticosterone was given again in dose of 5 mg a day. After eight days the cortin was discontinued, and the dose of sodium chloride by mouth was set at 8 gm per day. Three weeks after admission, her general clinical condition was good. Her weight was 128 pounds (58.1 kg), blood pressure 114 mm Hg systolic and 68 mm diastolic, hematocrit 33 per cent, blood sodium 140.9 me/L, and chlorides 109 me/L. On January 18, five weeks after admission, the salt intake was reduced to 4 grams a day. At that time her blood pressure and weight were being maintained, although her hematocrit ranged between 34-38 per cent. Although her appetite and strength had improved, she complained of occasional chest pain and non-productive cough.

On January 27 a trial with the sublingual preparation of desoxycorticosterone acetate in propylene glycol was begun. At the onset of this period her weight was 126 pounds (57.2 kg), hematocrit 38.5 per cent, blood pressure 106-116 mm Hg systolic and 60-80 mm diastolic, blood sodium 150 me/L, and chlorides 114 me/L. Five mg of the sublingual preparation were administered in a single dose each day for five days, and then 3 mg for two days. During this period there was no change in weight. The hematocrit fluctuated between 36 and 40 per cent, and the blood pressure showed no change until the last day when it suddenly fell to 80 mm Hg systolic and 60 mm diastolic, coincident with the development of marked weakness and anorexia, necessitating the discontinuance of the studies. She also complained of further cough and some dyspnea. After receiving 5 mg of desoxycorticosterone acetate intramuscularly, her blood sodium was 143.5 me/L and chlorides 106 me/L.

On January 9, after being on 3 mg of the synthetic hormone intramuscularly for five days, she suddenly developed fever, malaise, sore throat and increased cough. A throat culture demonstrated Beta hemolytic streptococci. The throat was red and granular with white follicles. The chest seemed clear. The white count was 12,000 with 80 per cent polymorphonuclear cells. The temperature rose to 105.2° F, and the blood pressure fell to 70 mm Hg systolic and 40 mm diastolic within a few hours of the onset of the acute illness. A continuous intravenous infusion of 5 per cent glucose in saline was started, and she was given 15 mg of desoxycorticosterone acetate in divided doses and 5 cc of cortin. With this, the blood pressure rose to 105 mm Hg systolic and 60 mm diastolic and the hematocrit was 36 per cent. However, she continued to run a spiking fever to over 105° F daily, became progressively less responsive, and her lungs became full of moist, bubbling râles. For this reason the salt intake was decreased by alternating the intravenous saline with glucose in distilled water. Fifteen mg of desoxycorticosterone acetate and 5 to 10 cc of cortin daily intravenously were continued, but despite this the blood pressure fell to 60 mm Hg systolic and 40 mm diastolic, and despite sulfapyridine intravenously, the temperature remained elevated to over 105° F, and dullness and bronchial breathing appeared over the right lower lobe. The patient died on the fourth day of the acute illness.

Postmortem examination revealed extensive bilateral caseous tuberculosis of the adrenals, fibrocaseous tuberculosis of the left upper lobe with recent bronchiogenic dissemination to the left upper and right upper lobes and hilar lymph nodes, calcified primary infection of the left upper lobe with calcified bronchial lymph node component, extensive focal and confluent bronchopneumonia of both lungs, marked edema of the lungs, fibrous obliteration of both pleural cavities, and diffuse brown pigmentation of the skin.

The patient's early response to therapy with the intramuscular desoxycorticosterone acetate was good. Preliminary observations with the sublingual preparation demonstrated that when administered in a single dose it was ineffective. Since it is probably incompletely absorbed and enters the blood at once, the inefficacy of a single dose is not surprising. The final fatal illness demonstrates again the low resistance these patients have, even when receiving presumably adequate replacement therapy, to infections which might, perhaps, not be serious in other individuals. The problems of therapy in this situation are apparent.

Case 9 S K, a 57-year-old housewife, had been treated at another hospital seven years previously because of abdominal pain and vomiting which had occurred intermittently for at least two years prior to admission. Five years ago she had had an episode of what she termed "shock" consisting of marked weakness and semiconsciousness. Four weeks before the present admission she had begun to feel progressively weaker with constant faint feelings, headache, palpitation, nausea, and vomiting. There was no history of tuberculosis. There had been some anorexia and a weight loss of 25 pounds in five years.

The physical examination revealed a dark-complexioned middle-aged woman who appeared very weak, was uncooperative, and resented examination. There were several small pigmented areas on the buccal mucous membranes. The lungs were clear, and the heart sounds were distant. The blood pressure could not be obtained by auscultation and was 60 mm. of mercury systolic by palpation. The reflexes were markedly diminished.

The urea nitrogen was 21 mg per cent, sodium 123 mEq/L, and chlorides 94 mEq/L. A glucose tolerance curve revealed a fasting blood sugar of 90 mg per cent,

half an hour later it was 160 mg per cent, one hour 180 mg per cent, two hours 95 mg per cent, and three hours 100 mg per cent

The roentgen-ray examination of the chest was negative. Roentgen-rays of the abdomen revealed irregular calcific deposits above the superior poles of each kidney, representing calcified adrenal glands

Treatment with 10 mg of desoxycorticosterone acetate intramuscularly and 8 to 12 grams of extra sodium chloride by mouth daily was begun on March 13. Within six days the blood pressure had risen from 54 mm Hg systolic and 36 mm diastolic to 106 mm systolic and 60 mm diastolic, the hematocrit had fallen to 26 per cent, and the blood sodium was 133.0 m e/L, chlorides 103 m e/L and the urea nitrogen 10 mg per cent. With this there was marked subjective improvement. She now took an interest in her surroundings and her appetite improved. For the next three weeks, except for a period when she was on a salt deprivation test, she was maintained on 5 mg of the synthetic hormone intramuscularly and 6 grams of salt daily by mouth. The blood pressure was maintained at about 100 mm Hg systolic and 50 mm diastolic, the blood electrolytes remained normal, and her weight was 120 pounds (54.5 kg). The hematocrit rose slowly to 33 per cent, in which range it has subsequently remained. On March 25-26, a salt deprivation test was carried out. On a sodium chloride intake of 34 milli-equivalents (about 2 gm) over a two day period she lost in her urine 186.9 milli-equivalents of sodium and 198.6 milli-equivalents of chloride, representing a considerable negative balance. Prior to the test, her blood sodium was 132 m e/L and chlorides 99 m e/L. At the conclusion, the blood sodium was 135.9 m e/L and chlorides 99 m e/L. At this time she complained of increased weakness, and her blood pressure fell to 90 mm Hg systolic and 58 mm diastolic.

After restabilization with 5 mg of synthetic hormone daily, a trial period on the sublingual preparation of desoxycorticosterone acetate in propylene glycol was begun on April 8, four weeks after admission. After one week, in which she received 5 mg in divided doses daily, her weight had fallen from 122 pounds to 118 pounds, her hematocrit had risen from 33 per cent to 37 per cent, although the blood pressure had increased to about 110 mm Hg systolic and 70 mm diastolic and the blood sodium was 133.4 m e/L and chloride 105 m e/L. However, on the same dose of hormone and salt by mouth her weight spontaneously rose to 121 pounds and her hematocrit fell to 33 per cent in the course of another week. For this reason the sublingual dose of hormone was reduced to 2.5 mg in divided doses for five days, again with no change in her status. All hormone was then discontinued, and she received only 6 gm of added sodium chloride by mouth daily for nine days. Except for a slight fall in blood pressure to 92 mm Hg systolic and 50 mm diastolic there was no change in her status, her weight being 122 pounds, hematocrit 33 per cent, blood sodium 133.3 m e/L and chlorides 104 m e/L. Although it was thereby demonstrated that she could be maintained on salt alone, it was felt advisable to use small doses of desoxycorticosterone acetate, so she received 1 mg intramuscularly every other day. One week after starting this regime, her hematocrit had fallen to 29 per cent and her blood sodium was 130.5 m e/L and chlorides 94 m e/L.

On May 21, about three weeks after having been restabilized, she suddenly developed fever, malaise, urticaria, herpes labialis and eosinophilia. The fever rapidly subsided, but the hormone was temporarily increased at this time. She was found to be sensitive to a number of plant inhalants and foods. After being taught to administer the medication herself she was discharged on June 3, taking 3 mg every other day and 6 grams of salt a day. On June 18 her weight was 127 pounds, blood pressure 100 mm Hg systolic and 60 mm diastolic, blood sodium 142 m e/L, and chlorides 108 m e/L. One month later her weight was 128.5 pounds, her blood pressure 124 mm Hg systolic and 76 mm diastolic, and it was found she could be maintained adequately on only 1 mg of the hormone twice a week. She was now having frequent episodes

of urticaria, and was found to be sensitive to the sesame oil which is the vehicle for the desoxycorticosterone acetate. For this reason some other form of therapy, such as pellet implantation, will be necessary in the future.

This woman, who undoubtedly had been suffering from adrenal insufficiency for some years and had finally reached a critical state before the true nature of her illness was established, showed a remarkable response to therapy. Because of the patient's age, the status of her cardiovascular system, and the prolonged hypotension, extreme caution was used in the administration of the hormone. That this was justified is apparent from the small dose necessary to maintain her after stabilization. No definite difference was noted between the response to the sublingual preparation plus salt and salt alone. However, it should be pointed out that, while the requirement for hormone is still changing, it is impossible to compare adequately different types of therapy. The occurrence of allergic reactions to the sesame oil has been reported before, and is an indication for either changing the oily vehicle for the hormone or the mode of administration.

COMMENT

Our experiences with the treatment of Addison's disease with desoxycorticosterone acetate during the past two and a half years have demonstrated that, provided proper precautions are taken, excellent results may be achieved. Not only are the abnormalities in electrolyte balance and blood pressure regulation completely alleviated, but there is usually a striking improvement in the strength and well-being of the patient, so that they can often return to their former occupations. It is now clear that failure to obtain improvement is usually attributable to either insufficient dosage or overdosage of hormone, or to the fact that the patient's symptoms are due predominantly to disturbances in carbohydrate metabolism.

In properly chosen and previously regulated patients the most satisfactory and economical method of treatment is by implantation of pellets. We feel that it is wiser, however, to implant less than the required number of pellets and to supplement treatment with some additional salt by mouth daily. In this way the dangers of unfortunate complications are lessened. By the sublingual route the hormone is definitely effective, but larger doses are needed than by the intramuscular route to produce equivalent results. Since by this method the hormone must be absorbed rapidly into the blood stream, it probably acts over a short period of time. For this reason it should be administered in small, frequent doses in order to produce an even effect. The ideal method of therapy is one in which there is a slow, steady release of hormone all day, a result which is best achieved by pellet implantation.

In order to obtain satisfactory results by pellet implantation, we feel that a prolonged period of observation while on treatment by the intramuscular route is necessary before implantation is carried out. During the first few months of treatment of a patient with the synthetic hormone, a gradual de-

crease in his requirement occurs. If pellets are implanted before the minimal requirement has been achieved, what was an adequate dose at the time of implantation will prove to be a toxic dose several months later. We now recommend that the patient be taught to administer the hormone himself and that he treat himself under home conditions for two to three months, using a small amount of added salt (5 to 6 grams). He should be seen at frequent intervals so that the dose of hormone can be promptly reduced on the appearance of hypertension, excessive gain in weight, or fall in hematocrit, these determinations being the most simple and reliable guides to therapy. When the smallest dose of hormone which will maintain the patient over a reasonable period of time has been determined pellets may be implanted. The number of pellets to implant is calculated on the basis that each pellet yields approximately 0.3 mg. a day, and the requirement by pellet is about 60 per cent of that required by the intramuscular route. Pellets of approximately 125 mg. in size should last about 11 months. In most cases exhaustion of the pellets is readily detectable by the gradual development of signs and symptoms of adrenal insufficiency. Reimplantation is simple, only a brief period of observation with the equivalent dose of hormone intramuscularly being necessary to demonstrate whether the requirement has changed. In those patients in whom a very small requirement of hormone is demonstrated, particularly if they are in the older age group, treatment with pellets is not advised because of the difficulty of controlling toxic reactions.

Toxic reactions, which were frequent early in our experience, were largely avoided later by extreme caution in the dose of hormone used. No fatal or life threatening reactions occurred. Hypertension, in one case accompanied by angina pectoris, was the most serious complication and occurred in four cases. The hypertension often did not appear until the patient had been receiving the hormone for some time, and often persisted for some time after the dose had been reduced. It did not seem to be correlated with the degree of salt and water retention. Elimination of the added salt or administration of potassium salts had little influence on the hypertension in our experience. In all cases the desoxycorticosterone had to be appreciably reduced and pellets removed if already implanted. Edema occurred at one time or another in four patients, and in only one was associated with any evidences of cardiac failure (case 2). Overdosage in some patients was characterized by weakness, malaise, headache, anorexia, salt distaste, and in one case (3) by eventual weight loss, probably due to decreased caloric intake. These symptoms are often difficult to differentiate from those of adrenal insufficiency. Three patients (cases 2, 6, 7) have developed palpable livers without evidence of cardiac failure or edema. The significance of this is not known. An allergic reaction in the form of urticaria was noted in one patient and this was demonstrated to be due to sesame oil, the vehicle for the desoxycorticosterone acetate. A different mode of therapy will, therefore, be necessary.

Seven of the eight patients have shown symptoms of hypoglycemia at some time while under treatment. In none have there been any appreciable changes in the glucose tolerance curve after therapy with desoxycorticosterone. In one case the symptoms were of sufficient severity to require the administration of cortin for their control. Another patient (not reported here, but who will be reported in detail by G Engel and Margolin), whose adrenal disease was characterized preëminently by chronic hypoglycemia and neuropsychiatric manifestations, could not be managed at all with desoxycorticosterone acetate. In this type of case cortin may be preferable.

Two patients developed serious intercurrent infections, one terminating fatally. Two other patients successfully weathered severe upper respiratory infections. In the management of these complications we must again emphasize the importance of carefully regulating the doses of desoxycorticosterone acetate and saline lest the burden of cardiac failure be added. In the presence of severe crises, it may be necessary to use cortin intravenously in addition to other measures, since the only solutions of the synthetic hormone can only be used intramuscularly.

SUMMARY

1 Eight patients with Addison's disease were treated with intramuscular injections of desoxycorticosterone acetate in oil.

2 In six of these patients implantations of pellets of crystalline desoxycorticosterone were performed, two of these have had three implantations and one has had two. The value of this method of therapy is pointed out.

3 Use of desoxycorticosterone acetate in propylene glycol sublingually in four patients demonstrated that this preparation is not as effective as either the hormone in oil or pellets.

4 The technic of preparing patients for implantation of pellets and the importance of prolonged observation before implantation are emphasized.

5 The nature of the toxic reactions from desoxycorticosterone acetate and the methods of avoiding them are discussed.

6 The failure of desoxycorticosterone acetate to influence the disturbances in carbohydrate metabolism is again confirmed and the importance of hypoglycemic reactions emphasized.

7 Serious intercurrent infections occurred in two patients, one terminating fatally. The management of these complications is discussed.

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DEFORMITIES OF THE THORACIC SPINE AS A CAUSE OF ANGINOID PAIN *

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DURING the past 25 years considerable attention has been focused on the possibility of dorsal root pain simulating attacks of angina pectoris, and many suggestions concerning the differential diagnosis of both have been offered. From the time angina pectoris was recognized as a distinctive and important syndrome, many observers have cautioned against confusing it with similar complaints. In 1915 Allbutt¹ in his extensive monograph on arterial disease and angina pectoris, stressed the importance of distinguishing "true angina" from a host of other symptoms and from "nervous squalls." However, Sir James Mackenzie's² clear descriptions of cardiac pain widened the horizon, and led the way toward a more exact differentiation between angina and angina-like pain. In recent years more extensive observations in this field have been recorded. Gunther and Sampson³ drew attention to the similarity between heart pain and the referred pain of root irritation in hypertrophic spondylitis. In an analysis of 50 cases they found that dorsal root pain may be projected around the chest or confined to one spot on the anterior chest wall, the pains might be paroxysmal in nature, and occasionally might be simultaneously noted in one or both arms. They felt they were able to draw well defined differences between real angina pectoris and dorsal root pain. Nachlas⁴ noted that seizures of anterior thoracic pain might be due to osteoarthritis of the cervical spine, provoked by certain movements or quirks of the neck. He reasoned that irritation of nerves of the brachial plexus may produce such pain by referring it along motor nerves, particularly those innervating the pectoralis major and minor muscles. The importance of differentiating the pain of angina pectoris from the referred pain of spinal arthritis was again emphasized by Pardee⁵ and by Fenn⁶. In addition, they pointed out that conditions such as diaphragmatic herniae, mediastinal tumor, herpes zoster and others may produce anginoid pain. Willius⁷ stated that anginoid dorsal root pain may become pronounced when the patient with hypertrophic spondylitis is reclining, and a considerable degree of spinal relaxation is effected. Reid⁷ found in a number of cases that cervical rib or a scalenus anticus syndrome induced root pain closely resembling angina. A case was recounted by Veil⁸ of a woman suffering from cellulitis of the left breast, with concomitant substernal oppression which cleared up on eradication of the cellulitis. Others^{10, 11, 12, 13} have drawn attention to the rôle of individual hyper- and hyposensitivity to pain, of the heart pains ac-

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accompanying fatigue and neurocirculatory asthenia, and of migraine, in the production of diagnostically confusing precordial distress. Most recently, Kellgren¹⁴ has again reviewed the question and has cautioned against mistaking somatic pain, occurring about the chest, for angina pectoris.

CLINICAL OBSERVATIONS

During the past nine months we have observed 15 patients whose symptoms simulated angina, but were considered of dorsal root origin. To restate the clinical problem, four of these cases are reported in brief.

CASE REPORTS

Case 1 McN, a 74-year-old farmer, entered Barnes Hospital in November, 1940 with the complaint of having had paroxysms of lower thoracic and upper abdominal pain for four years. He explained that the attacks were "really not pains, but feelings of discomfort or 'pressing' sensations." Attacks lasted from a minute to half an hour. On only one occasion was pain felt in the left shoulder and inner aspect of the left arm. The bouts were not related to meals, but were prone to occur at night especially when the patient felt chilly. Identical attacks were at times induced by such activities as shoveling, or exertions involving the upper extremities and trunk. Walking, running, or walking up a hill in a cold wind had never precipitated an attack. The patient's physician had considered this a case of angina pectoris and had treated it as such. Nitrites had been administered with indifferent results.

The past history was essentially negative except for the occurrence of a compression fracture of the twelfth thoracic vertebra 50 years before. This had healed at the time without complications.

Examination showed a tall, slender, well-preserved old man. There was a moderate senile emphysema. The heart was of normal size, with heart sounds distant but of "good quality." A blood pressure of 160 mm Hg systolic and 85-80 mm diastolic (lying) was recorded. The peripheral arteries were moderately thickened. There were no important abdominal findings. The spine was stiff and straight, showing a moderate lumbar kyphosis and flattening of the thoracic segment. Definite limitation of movement was noted in all parts of the vertebral column.

Routine laboratory tests were negative. Electrocardiographic studies showed no abnormalities. Roentgen-ray films of the entire vertebral column revealed a "moderate" osteoarthritis in all of the spinal segments, there was evidence of an old compression fracture of the twelfth dorsal vertebra. A chest film confirmed the clinical impression of cardiac size, in addition, moderate tortuosity of the aorta was shown.

The patient was seen by Dr. Frank Ewerhardt, under whose supervision a "cold water immersion test" (five minutes) was given. On the first occasion exposure to cold water reproduced a typical, transient attack of pain. Several days later the same treatment did not provoke an attack. An "articulator" was also applied to produce gentle traction on the spine. Stretching to a degree producing mild general discomfort induced an attack of paroxysmal lower thoracic pain, identical to those he had experienced spontaneously.

Case 2 C G, a 58-year-old clergyman, entered Barnes Hospital in January, 1941 complaining of attacks of upper substernal pain. Two weeks before entry, while walking up a gentle slope to his home, he suffered the first attack of a painful sensation which he said felt like breathing cold air beneath the upper sternum. This did not

radiate The pain was present for about one-half hour and disappeared on rest Two days later, while sitting quietly, he had an attack of severe substernal pain which was noted also to occur along the inner aspect of both arms Since that time there had been an attack every day The bouts of pain usually appeared when the patient was sitting Occasionally they occurred after meals With the exception of the first seizure, exertion had not been noted to bring them on The discomfort was usually a pressing sensation, not true pain, appreciated subinternally and across the anterior surface of the upper chest Ordinarily there was no radiation The patient took nitroglycerin with each attack, but on no occasion did the drug relieve the pain

Examination showed a large, rather obese man The chest was barrel-shaped, the abdomen markedly protuberant There was marked lordosis of the lumbar spine, and a definite, though not extreme, dorsal kyphosis Motion of the spine was everywhere definitely limited The apex beat of the heart was in the fifth intercostal space, 2 cm outside the midclavicular line, the heart was considered slightly enlarged The heart sounds were distant, but of "good quality" The blood pressure was 120 mm Hg systolic and 75 mm diastolic (lying)

Electrocardiographic studies showed evidence of myocardial change, in that the T-waves were altered in all leads A chest film showed a thoracic cage that was very large, partly due to emphysema The heart seemed to be slightly enlarged A spinal film showed some hipping and spurring of the sixth, seventh, and eighth cervical vertebrae

During the patient's stay in the hospital the severest attacks of substernal pain occurred while he was in bed, frequently at night These attacks were not relieved by the administration of nitrites Walking, stair climbing, and graded exercises did not precipitate pain This patient was seen by the neurologist, Dr S I Schwab, who believed that these were attacks of dorsal root pain due to hypertrophic spondylitis

Case 3 M G, a 45-year-old housewife, was seen in November, 1940, because of attacks of precordial distress and right costal margin pain which had occurred for the first time a month previously Specifically, these attacks were characterized by sensations of oppression subinternally and over the precordium with concomitant sharp knife-like pain extending from the back, along the left costal border There was no radiation The first episode occurred while the patient was at rest A physician told her she was suffering a heart attack, and ordered her to remain at bed rest for a month Subsequently the attacks of pain occurred several times each day, usually when the subject was doing her housework, but occasionally when she was lying down In a few instances tingling sensations were felt in the left hand during an attack The patient had been slightly short of breath on moderate exertion, but at no time was she orthopneic Cyanosis and dependent edema had not been noted Nitrites administered during the attacks gave indifferent results

Physical examination showed a well-developed, well-nourished middle-aged woman The interesting physical findings were limited to the spine which showed a definite moderate kyphosis, the greatest degree of flexion occurring in the sixth, seventh, and eighth dorsal segments, with limitation of all motion in the entire vertebral column The heart was not enlarged The sounds were of good quality The blood pressure was recorded as 112 mm Hg systolic and 70 mm diastolic The lungs were clear There was an area of definite cutaneous hyperesthesia sharply localized about the cardiac apical region

A number of electrocardiograms were taken during the time she was observed, all of which were within strictly normal limits Fluoroscopy showed no enlargement of the heart, the lung fields were clear Roentgen-ray films of the vertebral column (AP) gave no evidence of injury, small spurs in the mid-dorsal segments were attributed to hypertrophic change

This patient was given a Taylor brace and an abdominal support, and was instructed to use a hard mattress when lying down for rest or sleep. The attacks of anterior chest pain almost immediately disappeared and have not recurred to date.

Case 4 M. H. was a 76-year-old, single, white woman, who had been a governess and practical nurse, and was first seen in November, 1940. She stated that for four years she had had paroxysms of pain, beginning at the precordium, and rapidly spreading to the shoulders, arms, and back. The precordial distress was likened to a feeling of heavy weight, concomitantly an indefinable sensation occurred in both shoulders radiating along the medial aspect of the arms to the elbows. Sharp, interscapular backache occurred simultaneously. As a rule such an episode of pain lasted for several minutes, but on several occasions had remained an hour or more. Between attacks there was precordial tenderness and mild pain in the shoulders on motion. These paroxysms usually came on at night while changing position in bed, though occasionally exertion such as climbing stairs precipitated them. A physician had considered this a case of angina pectoris and had advised the administration of nitroglycerin during an attack. When the drug was taken during the paroxysm slight relief was promptly gained, the attack was completely dispelled in 15 to 20 minutes, the patient insisted.

Examination showed a well nourished, aged woman. The upper thoracic spine exhibited a marked, though not extreme kyphosis, with definite limitation of motion. The head was carried forward and the lumbar spine showed the indenture of lordosis. The vertebral column thus assumed the shape of a well defined letter S. The ribs had been displaced upward and outward to form a barrel-chest. Heberden's nodes were prominent, and slight crepitus could be elicited in the shoulder joints on passive movement. On physical examination the heart was considered questionably enlarged. The heart sounds were distant but of good tone, a blowing systolic murmur was heard at the apex. The blood pressure was 150 mm Hg systolic and 80-70 mm diastolic (lying). The lungs were clear, and there were no objective evidences of cardiac failure. There were no definite cutaneous sensory defects.

Electrocardiograms showed diphasic T-waves in I, II and IV G, with depression of the S-T segment in I and IV, and "coving" in Lead III. It was interpreted as showing myocardial damage of coronary type. Spinal roentgen-ray films showed only very slight lipping and spurring about the vertebral margins, in addition to the gross changes in contour noted before. Other laboratory findings were negative.

Because of the character of the pain, its extreme irregularity of duration, and the circumstances usually precipitating it, the weight of evidence pointed toward dorsal root pain, despite the presence of probable coronary heart disease.

A specially made brace was applied to the shoulders and back in an effort to improve posture, and in addition her bed was equipped with hard mattress and fracture-boards. Following this no attacks occurred on exertion. For a month after the use of a hard bed was begun she continued to have paroxysms of pain at night. More recently these had diminished in severity, and for the past four weeks had been entirely absent.

The recognition of pain attributable to disease of the vertebral column is difficult, and in our limited series we have encountered the same doubts and obstacles as have been emphasized by many who have previously considered the problem. The symptoms of all of our cases resemble those of angina pectoris. Some features of the pain, its occurrence on exertion, its occasional short duration, and the partial relief often accomplished by the use of nitrites are suggestive of a cardiac origin. The majority of our patients described sharp pains in the back or elsewhere in the chest occurring simul-

taneously with precordial distress. Careful analysis of the symptoms usually revealed that the feeling of oppression beneath the sternum was superficial, and that the choking or strangling sensations so characteristic of true anginal attacks were absent.

Another possible differentiating point is the duration of the episodes of pain, which in some of our cases was greater than could reasonably be expected in true angina.

It seemed curious that many of these individuals obtained transient relief of symptoms on receiving nitrites. On the advice of their physicians, most of them carried nitroglycerin for use in the event of a seizure. The remission of symptoms resulting from this medication was not so complete as in angina pectoris, and frequently the pain gradually reintensified as the effect of the nitroglycerin diminished. There were occasions when the same patient experienced no relief from the drug. If indeed these patients were suffering from spinal nerve irritation, it appeared so doubtful that the discomfort could be relieved by such medication that we were inclined to believe the effect might have been psychogenic.

In order to investigate this question further, however, a number of patients, with painful osteoarthritis and rheumatoid arthritis and with myalgias, were given single doses of nitroglycerin without being told what to expect. When the apparent maximum effect was attained active and passive motions of the joints were performed and the myalgic patients were asked to move the painful muscles. More than half of these subjects stated that they experienced some relief during the height of nitrite action when painful joints were manipulated, in some this relief was fleeting, whereas in others the remission was definite, if transitory. It is difficult to assign a reason for this effect. Dixon⁹ stated that he had noted relief of pain due to fibrositis by the use of nitrites. It is a common experience that heat, an active vasodilator, may confer temporary benefit on individuals with arthritis when locally applied. Rubifacients and other drugs promoting vasodilatation may accomplish the same. The simplest plausible explanation might appear to lie in the marked vasodilatation brought about by the nitrites. It would seem possible that by such influence the pain arising from mechanical pressure or by chronic inflammation might be temporarily allayed. The explanation is possibly less important than the realization that relief by nitrite medication may lead to diagnostic error.

Roentgenological studies of the vertebral column were not always helpful in establishing the diagnosis. In the cases reported only moderate osteoarthritis could be demonstrated. It seemed probable that the location rather than the extent of the bony change is determinant in causing irritation of the spinal nerves, and that pathological changes about the intervertebral foramina, not easily seen even in detail films, may be responsible for severe symptoms.

More significant than the roentgen-ray studies were postural defects which were evident in all of the patients of the group, and which were

attributable to disease of the vertebral column. In some there was straightening and stiffening of the dorsal spinal segment with limitation of motion, in others there was dorsal kyphosis of varying degree with markedly decreased movement of the spine.

In considering these cases it was realized, however, that such defects are extremely common, and that even when they are more evident and advanced, they are often asymptomatic.

The mechanism by which dorsal root stimulation is produced by hypertrophic spondylitis or other spinal deformity has not been satisfactorily explained. Usually ample attention has been paid to the character and distribution of the referred pain,^{2, 3, 4, 15, 16} but the circumstances that may provoke it and the mechanics that operate to irritate the nerves have been but superficially considered or have not been mentioned at all. Nevertheless, a few reports have appeared from time to time which strike at the more basic aspect of the problem. Some years ago Sicard¹⁷ spoke of funiculitis and radiculitis in the pains of lumbago and chronic postural errors. More recently Oppenheimer¹⁸ has held that patients may develop segmental neuritis from crushing of nerve-roots caused by thinning of intervertebral discs and collapse of the intervertebral foramina. Morton¹⁹ believed that diminution of the size of the intervertebral foramina was more common than thought. Others^{20, 21, 22} have felt that osteophytosis frequently occurs about the transverse processes, spines and foramina which may irritate the roots on movement of the bones.

From the clinical standpoint most cases with anginoid pain show only moderate roentgenologically recognizable changes in the spine. Key²³ believes that in most instances of this type there is insufficient osteophytosis in the region of the nerve-roots to account for dorsal root irritation. However, in the clinical case the pain distribution over the chest and abdominal wall and the frequency with which movement of certain character produces it suggest that the irritation, from whatever cause, may be sharply localized in one or more spinal segments. As stated before, the physical sign that was constant in these cases was some postural deformity involving the vertebral column. That postural defects alone should in some way cause stimulation of the posterior roots at first seemed highly conjectural, however, on consideration of the anatomic relationships of vertebral column,²⁴ spinal radicles and the intercostal nerves, the question arose whether chronic deformities of the spine and thoracic cage might not exert traction on the nerves. Impingement of the nerve fibers in coursing through the intervertebral foramina, or tension at their connections with the spinal cord, might occur, with stimulation particularly of the sensory portion. It seemed possible that this might explain the curious neurologic picture in the presence of postural defects, where there was so little objective evidence of spinal disease. Therefore, an attempt was made to study the spinal nerves *in situ* in an effort to uncover more information as to the underlying cause of these clinical symptoms.

EXPERIMENTAL OBSERVATIONS

On a cadaver the large muscles of the back were removed in such a manner as to uncover completely the posterior thoracic wall and vertebral column. The posterior portions of the neural arches were removed, and the dura mater was incised longitudinally, the edges being held back by means of hooks. In this way the spinal cord and nerves from the sixth cervical to the

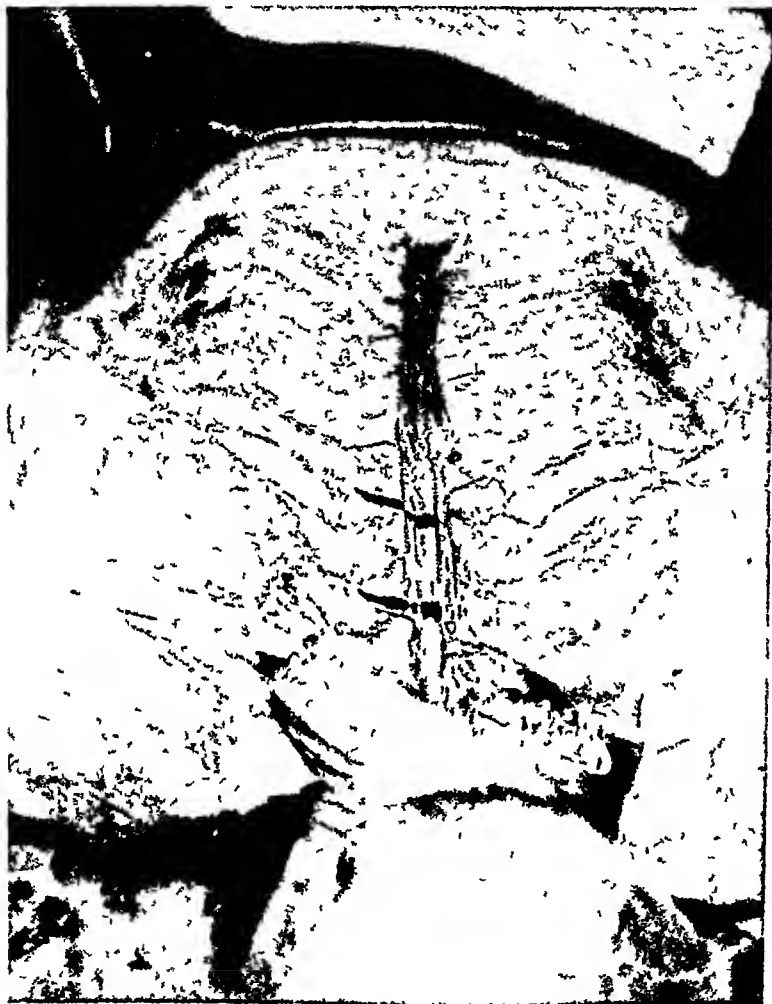


FIG 1 The exposed spinal canal of the cadaver lying prone and with a normal curvature of the spine. Note the reference points (black lines) across cord, meninges and adjacent bones.

first lumbar vertebra were exposed. The contents of the thorax were next removed to gain access to the vertebral column anteriorly. In order to produce an artificial "kyphosis," wedge-shaped clefts were made in the anterior portions of the vertebral discs and bodies of the five upper dorsal segments. Care was taken to leave uninjured the articular structures between the vertebrae themselves, the clefts were sufficiently shallow so that no portion of the spinal canal was exposed anteriorly. This arrangement allowed the upper thoracic spine to be flexed abnormally to a position of extreme kyphosis.

It was found convenient to change the curvature of the spine by laying the cadaver prone, a rod was then passed under the thorax to the ends of which cords were attached and passed over pulleys in the ceiling and the opposite ends weighted. By this arrangement the thorax could be raised from the table, the upper thoracic spine falling downward in a marked "kyphosis." Horizontal traction to the head produced abnormal straightening of the spine.



FIG 2 Horizontal traction has been applied to the head of the cadaver to render the vertebral column abnormally straight. Note that the second reference point on the cord (caudad) has been displaced toward the head so that a stretch is applied to the spinal nerves (not shown).

The use of this dissection permitted direct study of changes of relationship and tensions applied to the spinal nerves during extreme flexion and extension of the vertebral column.

With the cadaver lying prone, without traction on the chest or neck, the curvature of the spine was essentially normal. The positions of the spinal nerves and the corresponding segments of the cord were noted in relation to the vertebrae and to the intervertebral foramina from which the nerves find exit. Horizontal traction was then applied to the head. As the spine

straightened, eliminating the normal dorsal curvature, the cord was placed under tension so that the reference points on the cord were displaced cephalad by 3 to 4 mm. Actually in straightening the spinal canal, there was an absolute displacement caudad of the vertebrae with reference to the cord. Such displacement would be expected to exert tension on the spinal nerve roots which would be particularly severe in two places: first at the



FIG 3 The thorax of the cadaver has been lifted upward with collapse forward of the bodies of the upper dorsal vertebrae, producing a position of severe kyphosis. The reference lines on the spinal cord have been drawn markedly cephalad, placing extreme tension on the spinal nerves both at their attachments to the cord and at their angulation through the intervertebral foramina.

origins of the roots from the cord, and secondly at the portion of the root angulated in passage through the foramen. Palpation of the spinal nerves in this position showed them to be very much more taut than when in normal position. On release of traction to the head, the spinal column again resumed its normal curve so that the cord and nerves lay at their original vertebral levels.

Essentially the same degree of cord "displacement" was noted when artificial kyphosis was produced. It should be remembered that the articulations between the vertebrae were kept intact so that the kyphosis occurred by virtue of a closer approximation of the anterior surfaces of the bodies. When this was accomplished by raising the cadaver from the table the segments of the cord occupied a position relatively higher in the spinal canal. As in the former case, tension was thus applied to the spinal nerves because of their

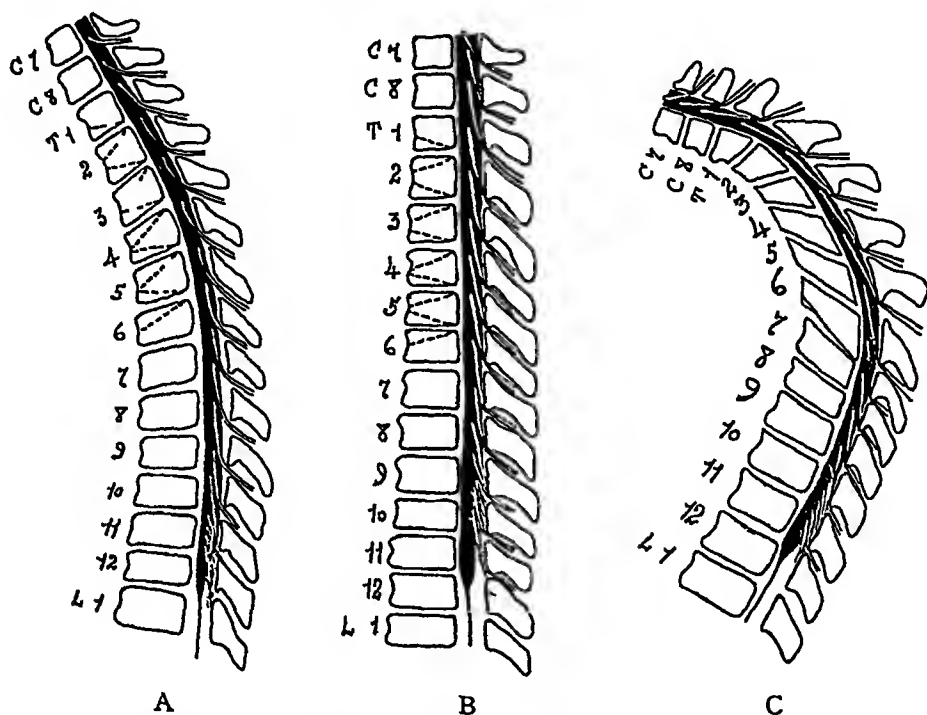


FIG 4 Diagrammatic sketches, in exaggeration, of the spinal column and cord. A shows the normal vertebral column in relation to the cord and spinal nerves. The dotted lines in the vertebral bodies of T1-6 indicated the wedge-shaped clefts of bone chiseled away to permit abnormal flexion. B illustrates the position of the cord within the spinal canal on abnormal straightening of the spine. The cord is displaced cephalad. C shows the vertebrae in abnormal flexion (marked kyphosis). The spinal canal is thus lengthened (cf text) and the cord again is drawn cephalad placing tension on the spinal nerves.

essential immobility at the intervertebral foramina, and this tension could be appreciated by palpation of the nerve filaments.

In the cadaver the displacement upward of the spinal cord when the vertebral column is either flexed or extended to an abnormal degree indicates that in either case the spinal canal is elongated. This becomes clear when one considers the mechanics. During hyperextension the vertebral bodies are separated and the articular facets between the vertebrae are separated as far as the ligaments will permit. In consequence of this, the cord is drawn cephalad. When the vertebral bodies are collapsed, and hyperflexion and "kyphosis" result, the spinal canal is again lengthened. The intervertebral discs function as cushions for the weight bearing bodies, and axes of the

intervertebral joints lie anterior to the bodies of the vertebrae. Therefore, hyperflexion (permitted by the wedge-shaped clefts) results in separation of the neural arches and subsequent elongation of the spinal canal. The relationship of the cord to the neural canal is thus changed as the cord is pulled cephalad, and tension on the spinal nerves is induced. The accompanying diagram shows, in exaggeration, these alterations in the level of the spinal cord.

DISCUSSION

It is, of course, questionable whether tension on the spinal nerves at their fusion with the cord reaches such a degree under conditions of life, for one might expect that the dura mater, a tough membrane enveloping the cord and extending along the spinal nerves to the intervertebral foramina, would bear the stretch and spare the spinal nerves as deformity of the spine developed. However effectively the dura might function in this regard, the change of position of the meninges and cord with respect to the vertebrae could hardly eliminate the longitudinal tension imposed on the intradural spinal nerves. The gradual tension of the spinal nerves alone, growing out of progressive deformity of the vertebral column, could hardly be expected to produce the clinical symptoms. Schmorl²⁵ studied in great detail the changes occurring in the intervertebral discs which give rise to spinal deformities. He showed that swelling of the nuclear part of the discs may occur with evulsion, later, of the nucleus pulposus into the spongy portions of the vertebral bodies to produce atrophy and thinning of the contiguous bone. Nodular and calcific deposits may then occur in the cartilage and about the bony surfaces. The spinal deformities occurring in the wake of such cartilaginous and bony changes were thoroughly reviewed by Kountz and Alexander²⁶. They showed that as swelling of the discs occurs the spine is abnormally straightened and stiffened. Progression of degenerative changes in the disc ultimately accomplishes thinning of the under- or overlying bone to such a degree that it can no longer support its burden, and collapse of the column at that point may occur. This results in kyphosis, which at first is slight, but later may become so extreme as to produce the common "hump." This process usually occurs in the upper dorsal portion of the vertebral column. In our cases it was during and after the time these alterations in spinal contour took place that clinical symptoms in the form of paroxysmal anterior thoracic and upper abdominal pain on motion apparently occurred. This also suggested the reason why, in so many instances, motion of a particular sort may precipitate the symptoms²⁷ and why they may show such a multiplicity of types.¹⁵ An additional interesting suggestion is found in the work of Crenyx.²⁷ Crenyx believed that degenerative changes in the intercostal muscles could be demonstrated by studying their response to electrical stimuli, and that such degenerative change, occurring with spinal deformities and emphysema, resulted in fixity of the

thoracic cage in the position of inspiration. If this were true, then further immobility of the intercostal muscles and nerves might subject the nerve roots to irritation on motion of the vertebrae. However, Kountz and Alexander²⁶ and Clement²⁸ felt that costal rigidity was more likely a result of bony deformity than a disease of intercostal muscles and nerves.

It was emphasized earlier that measures which improved the posture of our patients alleviated or abolished their discomfort. In this connection the work of Kerr²⁹ is of some interest. He approached the treatment of angina pectoris from a unique standpoint with the supposition that angina may be the result of myocardial anoxemia enhanced by faulty refilling of the heart, and hence diminished oxygen supply to vulnerable tissues. Many of his patients had exhibited impairment of diaphragmatic motion which he thought might further reduce the return flow of blood to the heart. Kerr applied abdominal belts to these patients, and sought improvement in posture. Many of his subjects improved under this régime. In the light of our experience, it seems possible that the improvement he noted may have been due to the correction of general posture. Gallavardin³⁰ stated that some cases of angina pectoris have a "collaring sensation," as of a portmanteau placed about the shoulders, radiating about the shoulder-girdle. The attacks, he noted, were transient or of long duration, and might be provoked by movements of the upper extremities. He further stated that such episodes were usually indifferently relieved by nitrites. It is possible that Gallavardin may have been dealing with a problem similar to ours.

SUMMARY AND CONCLUSIONS

Report has been made of four of 15 patients having anginoid pain attributable to spinal deformity. Frequently the seizures could be induced by movements involving the deranged spinal segments. Procedures applied in an effort to improve posture brought about improvement or cure of the symptoms.

The mechanism of the production of dorsal root irritation was considered in the light of clinical findings, and an experimental study was made in order to investigate the problem further. This was done by using a cadaver, with spinal cord and nerves exposed, in which an abnormal degree of spinal flexion and extension could be produced. When the spine was either flexed or, straightened to an abnormal degree, the spinal canal tended to become elongated so that the cord was drawn cephalad. This imposed tension on the spinal nerves particularly at their angulations through the spinal foramina and at their attachments to the cord. It was postulated that movement imposed on the nerves under such tension may give rise to irritation of the fibers with the production of referred pain.

Some of these patients experienced unexplained transient relief from the use of nitrites. It is emphasized that this phenomenon, if ignored, might lead to an incorrect diagnosis of angina pectoris.

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THE USE OF COLD IN MEDICINE*

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IN no period of medical history has so much progress been made in the conquest of disease as in the past few decades. One by one the infectious diseases have been pushed into the background, the deficiency diseases no longer pose major problems, even cancer, and the degenerative diseases of the cardiovascular renal system seem slowly to be losing out in their struggle for dominance over man. Scientific, specific bio- and chemotherapy have largely replaced the placebos, superstitions and nostrums of the past generation, yet the hot-water bottle and the ice-bag yield not one iota of their importance in our present-day therapeutic armamentarium.

It is my pleasant task to attempt to review the many uses which cold has found in medical practice. Just as in the case of heat, up until the past few years, hypothermy has been wholly a matter of local application to the superficial tissues, skin and mucous membranes. Only recently have attempts been made to reduce the entire body temperature as a therapeutic measure in various pathologic states, in a manner theoretically more or less analogous to the various forms of induced "fever" therapy so successfully employed in certain disorders. Obviously, it is too early entirely to evaluate the method, for it is frankly still in its experimental phases, and sufficient clinical data have not yet accumulated.

Before proceeding with the discussion of the therapeutic use of cold either locally or by the generalized reduction of body temperature to which have been applied various terms such as "refrigeration" and "hibernation" (Smith and Fay⁵⁹), cryotherapy (Gerster and Sauer²⁹), experimental hibernation (Vaughn⁶⁷), hypothermia (Talbot⁶²), and "frozen-sleep" (lay press), it might be well to review briefly some of the laboratory evidence upon which the use of reduced temperatures as a therapeutic agent is based. It should be stated at the outset that part of the evidence is contradictory and much further work will be necessary to clear up many of these discrepancies. Some of the difficulties may be technical, some of them may represent species differences, and some of them may be a matter of interpretation.

It is now some 10 years since Fay and Henny²⁴ first became interested in the problem of whether spinal cord lesions might produce localizing segmental dermatome temperature changes of diagnostic significance through a hyperemia comparable to that which follows experimental stimulation of the reflex arc by heat or pain. As so often happens in such a study, the original quest became submerged by observations of far greater fundamental importance. In this case the problem evoked related to the effect of differ-

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ences in temperature upon embryonal, and by analogy, upon malignant cell growth Geschickter and Copeland³⁰ had pointed out the well known fact that metastases from tumors were found chiefly in the warmer parts of the body. Primary tumors likewise were known to occur chiefly in the better vascularized, warmer areas, and to be rare below the elbows and knees as emphasized by Pack and his associates⁵⁰. Huggins, Noonan and Blockson^{36, 37} had recently demonstrated that the hematopoietic and reticulo-endothelial tissues of the rat's tail and extremities could be maintained in the same state of activity as those of the central bones merely by preventing their temperatures from falling below 95° F. Coghill¹⁵ had noted that the embryos of *Amblystoma punctatum* Cope, when subjected inadvertently to critical temperature levels during ice-box storage and subsequent incubation in every instance showed some maldevelopment. Smith and Fay⁵⁹ reported a similar finding in respect to chick embryos. If eggs were subjected to a critical temperature level of about 90° F. for the first 48 to 72 hours of incubation, and subsequently were incubated at 103° for the remainder of the normal 21-day incubation time, developmental defects of some degree would result with regularity.

On the strength of these various observations, some four years ago we advanced the theory, which was further supported to some extent by preliminary tissue culture studies, that there were differential metabolic requirements, or rather, different "critical" temperature levels for neoplastic as compared to adult differentiated cells⁵⁹. This is a fundamentally different concept from that relating to the effects produced by the actual freezing of cells or tissues, with which our studies have frequently been confused. Many investigators have explored this latter field with somewhat conflicting results. Breedis and Furth¹³ have conclusively shown that tumor cells could be preserved at —70° C. for periods of at least as long as a year provided, contrary to general opinion, that the freezing was permitted to take place slowly. Rahm⁵³ had the same experience with rotifers, nematodes and tardigrades, finding that with slow freezing they would survive temperatures of —253° C. Over 30 years ago Gaylord,²⁸ Michaelis,⁴⁴ and Moore and Walker⁴⁶ established the fact that Jensen's rat tumor would survive freezing in liquid air for as long as half an hour, and Ehrlich²² at about the same time was able to keep cancer cells alive at —8° C. for as long as two years. On the other hand, Ciarnier¹⁸ found no viable tumor cells in tissue cultures subjected three times to repeated freezing and thawing at temperature levels ranging from —20° C. to —40° C. Lambert³⁹ felt that cancer cells were more resistant to cold than were normal adult tissue cells. Auler⁵ and his associates in exposing animal tumor tissues to 0° C. found that most of the transplants would subsequently grow. Bischoff, Long and Rupp¹⁰ noted no permanent effect upon tumors in mice subjected to reduced body temperatures of as low as 19° C. (65° F.) for as long as 24 hours at a single time, or episodes of seven hours each, repeated four or five times.

Lucké,⁴¹ in working with frog tumors, both in the natural host and as transplanted into the anterior chamber of the eye, came to the conclusion that temperatures as low as 4° C were effective chiefly in influencing the rate of growth of the tumor, with subsidiary effects upon the form the growth took. These experiments were carried out with great care at 28° C, 7° C, and in one series of frogs subjected to hibernation, at 4° C for 10 weeks. They seem to confirm the hypothesis of the importance of an optimal temperature for successful tumor growth. They are open to the criticism that the frog tumor is one generally accepted as viral in nature, and it is well established that viruses are preserved, not destroyed by low temperatures. The experiments are likewise not entirely analogous in that they are dealing with cold-blooded, poikilothermic animals rather than homeothermic warm-blooded mammals. In general, they tend to confirm our observations as to the universality of such physical laws as relate to the thermodynamics of biology. Perhaps the most complete reviews concerning the resistance of cells to extremes of cold are the recent ones of Belehradek,⁷ Heilbrunn,³³ and Luyet and Gehenio.⁴²

Fuller, Brown and Mills²⁷ came to the conclusion that the incidence and rate of growth of tumors in mice was heightened by keeping the animals in a reduced environmental temperature. They further cite the influence of climate on the incidence of cancer in man as shown by the preponderance of cases in the northern as compared with the southern states in this country. They make one interesting and important comment, stating that, in their opinion, the chief factor involved relates to the lack of body surface radiation in the colder environment. They make no comment regarding the actual body temperature of the animals in their experiments. All of this harks back to one of our own earliest comments that there is an optimal level for the growth of all cells, speaking in terms of physical wave lengths, both in respect to light and temperature.

Statistics on the world distribution of cancer are far from satisfactory. Although lower morbidity and mortality figures seem to prevail in the tropics, we must attempt to correct for the age factor, with its low average age at death as compared to that of the United States as a whole of nearly 65 years. Do the increased metabolism of the warmer climate, the earlier adolescence, the earlier climacteric physiologically balance the added years of life in the temperate zones, so that the cancer incidence actually can be compared?

In view of one of the chief clinical problems encountered both by ourselves and others in the use of general hypothermy, that of a somewhat atypical form of circulatory failure which occasionally occurs, we have been particularly interested the past few months in studying the effects of hypothermy on tissue cultures of heart muscle with the object in view of finding methods of compensating apparent cardiac failure. We have found but little previous work on striated muscle cell cultures of any kind which seemed particularly pertinent to our problem. Moran⁴⁷ felt that —2° C repre-

sented a critical temperature level for normal frog muscle. Lake³⁸ found that -7°C was fatal for *in vitro* cultures of fetal rabbit heart. Hetherington and Craig³⁵ found the time factor was equal in importance to the reduced temperature in embryonic chick heart before explanting tissue.

In similar but rather more extensive studies^{55a} upon fetal heart cultures, we have been impressed by several findings which occurred with great regularity. In the first place, if fetal heart muscle is stored at varying reduced temperature levels from 37°C to 0°C for 24 hours before explanting into culture medium, there is a latent period before such fragments of heart muscle start growing and beating which may be expressed as an almost straight curve, proportional to the temperature. In the second place, if the time interval at which such heart muscle is stored is prolonged the survival period increases as the temperature approaches zero in spite of the fact that the latent period is prolonged. In the third place, as Hetherington and Craig³⁵ noted, the volume or mass of tissue influences the survival rate, the larger fragments showing greater resistance.

Of more interest, perhaps, are those observations relating directly to the influence of lowering the temperature upon the actual implanted fetal heart muscle tissue cultures. At 37°C the average survival period of normal active cell contractility and growth was about three weeks. At 27°C activity could be maintained regularly for periods of six weeks or more with no evidence of diminished functional capacity. Cultures submitted to a "critical" 22° to 24°C temperature level for periods up to four days would survive and convalesce but with progressively longer latent periods of up to 80 or more hours before functional activity was restored. Although the cultures themselves might, and usually did, survive a five-day period of "hibernation" at these levels, the cells individually as a mass showed no evidence of contractility during this time, nor did they recuperate functionally after restoration to the normal 37°C body temperature level.

Physiological observations, many of which it has been possible to record cinematographically, show that with lowering of the temperature of the culture, there is a marked prolongation of the interval between contractions (latent time). The contractile phase is much less strikingly affected until the lower temperature ranges are reached, or until there has been prolonged exposure at critical levels. Finally, it is of interest to note that fibrillation can be induced at will, by the rapid lowering of the temperature to near 0°C .

Tuttle's⁶⁶ recent observations of the effects of decreased temperature on the activity of intact skeletal muscle as studied physiologically in human beings bears out these tissue culture findings. He noted the same prolongation of the relaxation time and explains on physiological grounds, for the first time to my knowledge, the rationale of, and the necessity for, the familiar "warming-up" of athletes before, as he puts it, "explosive bouts of exercise."

Sano and Smith⁵⁵ noted that a "critical" level around 22° to 24°C existed in respect to the nuclear division of tumor cells in tissue culture, and

that only rarely would any tumor cells survive a period exceeding five days at a level of 20° C. By contrast,^{55b} they found that a temperature of 25° C was the optimal level in certain respects for the growth of fibroblasts in tissue culture. This they suggest may be of practical importance in wound healing, for the cells grow more compactly, with less collagen formation and, therefore, with less disfiguring and often, less painful scar tissue formation.

These general observations regarding the effects of reduced temperature upon cell growth and viability, although largely empiric and lacking almost entirely in respect to the finer details of cell respiration and metabolism, nevertheless seemed adequate to utilize as a basis for certain clinical observations.

LOCAL HYPOTHERMY

In the field of local hypothermy there has accumulated a vast experience and literature. As we have pointed out previously, Bennett⁸ in 1849, Arnott⁴ in 1851, Velpeau⁶⁸ in 1856 and Cooke¹⁷ in 1865, all commented favorably upon the use of brine mixtures in the treatment of accessible cancers such as those of the cervix and breast. It is of more than passing interest that they used hypothermy not only to destroy the growth locally, but also for its anesthetic effect. Again, in 1872 S. Wier Mitchell⁴⁵ commented on his experiences in the Civil War regarding the value of cold therapy in the treatment of the pain associated with nerve injuries. Lortat-Jacob and Solente⁴⁰ in 1930, in an extensive monograph, review their own experience as well as that of some 300 other authors with "cryotherapie," the emphasis being placed almost entirely upon carbon dioxide as the cold agent. Its value in the treatment of birthmarks, various nevi, basal cell carcinomata, certain carefully selected squamous carcinomata, as well as many of the inflammatory dermatitides and degenerative dermatoses, is particularly stressed.

Our own work in the cancer field, using cold applied locally at 4° C to 5° C (38° to 40° F), was begun in 1936 and has been carried on more or less continuously in a series of hopeless, inoperable terminal cases since that time. The clinical care of the cases has been under the direct supervision of Dr. Temple Fay and his associates. A committee made up of members of the various clinical and laboratory services has served in an advisory capacity in selecting cases, determining the type and extent of treatment, and in evaluating the results. A wide variety of types of tumor have been studied and reported both clinically^{23, 59} and pathologically^{55a}. They have included oral, esophageal, gastric, rectal, vesical, cervical and mammary cancer as well as brain tumors, bone sarcoma, lymphosarcoma, Hodgkin's disease and melanosarcoma. Regressive changes of variable degree have occurred regularly, even to the point of histological clearance of the local tumor bed in some few instances, as demonstrated by biopsy specimens taken at intervals during and following treatment.

In addition to the regressive changes noted in the tumors themselves, pain relief has been one of the most striking clinical results. This pain relief has not only occurred during the period of application of the cold, but in many cases has persisted for several days or even weeks following the removal of the cold as reported by Fay and McCravey²⁵. Not infrequently it has permitted the reduction or complete withdrawal of sedation. Thus, as Arnott⁴ so aptly put it nearly a century ago "even were the benefit (of local hypothermy) to be limited to this (relief of pain) alone, there are few "recent" medical discoveries which would exceed it in importance."

We have sought a physiological explanation of this phenomenon. In part the answer undoubtedly is supplied by actually cutting down the blood supply because of the vasoconstriction which accompanies the application of cold, thus reducing the familiar "stretch" mechanism upon the pain fibers. In part the answer may be expressed as a change in nerve conductivity through physico-chemical alteration of the lipoids by congelation. And, finally, the fact that cold acts as a true protoplasmic anesthetic, as recently suggested by Allen,² rounds out the concept.

As may be seen from these comments, the possibilities of local hypothermy in this one field of malignant disease alone require further extensive exploration and correlated study by laboratory and clinic alike. To us the evidence is convincing that local refrigeration has a very definite place in the therapeutic armamentarium of cancer. In our present state of knowledge, surgery is still the backbone of cancer treatment. Supplementing surgery, and in certain specific types of cancer, even replacing surgery as the method of therapeutic choice, is irradiation. But irradiation is by no means the panacea we had hoped it might prove to be, and as an adjunct to both surgery and irradiation, hypothermy has much to offer, especially in the management of the terminal stages of the disease, altogether aside from any possible curative value it may possess. In the control of pain, in reducing narcotic requirements, in its bacteriostatic effect and resultant deodorant action, it makes life very much more bearable for the patient as well as simplifying the nursing problem. Through the almost invariable gross shrinking of the tumor mass often within 24 to 48 hours as a result of the vasoconstriction which occurs, with the consequent reduction in edema, not only of the tumor but also of the surrounding tissues, it may well provide a better opportunity for maximal irradiation effect in certain instances in which radium implantation is to be employed, as in cancer of the uterus. As is well known by the physicists, and constantly emphasized in our tumor clinic by our radiologist, Dr. W. E. Chamberlain,* the effective dosage of radium diminishes roughly as the square root of the distance from the point of application. Thus, reducing the volume of the tumor by preliminary hypothermia should tend to improve the chances of reaching the more distant cells with an adequate irradiation dosage. Furthermore, there is a rather widely held view that

* Personal communication

tumor cells are more readily damaged during the period of mitosis. It has been shown by Sano and Smith⁵³ that a rather large proportion of tumor cells grown at the "critical" level of 22° C to 24° C tend to show "arrested," incomplete mitosis. Combining irradiation therapy with such hypothermia might well increase the effectiveness of both procedures, arguing on purely theoretical grounds. Thus far very few pertinent observations in respect to such possibilities have emanated from the laboratory. Breedis and Furth¹² have shown incidentally, in an experiment designed to prove that there was no virus element present in their tumor cultures preserved at —70° C, that radiation in well established effective dosage at normal temperature levels was equally effective at this subnormal level. On the other hand, Cook¹⁸ demonstrated that *Ascaris* eggs exposed to a dosage of 5000 roentgens and then preserved at 5° C for eight weeks developed 45 per cent normal embryos, whereas those eggs which were permitted to develop immediately at 25° following irradiation produced only 1 to 2 per cent normal embryos. They conclude accordingly that low temperature has a definite and beneficial effect upon the recovery from irradiation effects. Obviously the experimental factors are not strictly analogous, as the radiation was given first in this case.

Thus far my comments on the use of local hypothermy have related almost entirely to the field of malignant disease. You will perhaps excuse me for this in the realization that our primary interest and efforts have been pointed in this direction, with the hope that others would see its further possibilities and explore those fields in which their particular interests lay.

In connection with various pain problems Fay²³ has found local as well as general hypothermy of definite clinical value. In intractable types of headache, application of a cooling hood has almost regularly given prompt relief. Here we see the modern, streamlined version of the ice-bag, with accurately controlled temperature regulation. Similarly, the use of a cooling pad over the lower thoracic and lumbar regions is effective to a surprising degree in controlling lower abdominal and pelvic pain, apparently through reduced conductivity of pain impulses by the refrigeration effect upon the posterior roots, thus breaking the continuity of the reflex arc. Undoubtedly, the time honored use of the ice-bag on the abdominal wall over the appendix region depends upon a similar reflex action. It seems unlikely that the penetrating effect of cold applied locally to a thick abdominal wall could actually cause regression of the inflammatory process in the appendix by a true refrigeration effect, yet Selden⁵⁶ found a drop in temperature of as much as 7.5° F to 15.6° F in the subjacent intraperitoneal areas after 30 minutes of such application. Bierman and Friedlander,⁹ in discussing the penetrative effect of cold, found that in the human being cold applied as ice bags to the calf of the leg for periods ranging from one and a half to two hours caused a temperature drop of the muscle two inches beneath the surface, of as much as 15° to 26.4° as recorded by thermocouple. The temperature of the male urethra was lowered as much as 23.8° F in an hour and a half by applying

cold through a metal applicator in the rectum. Similar drops of temperature were observed in the rectum when water at 44° F was circulated through such an applicator introduced into the vagina. In our own studies these observations have been confirmed time and time again, so far as the immediately adjacent tissues are concerned, but the refrigeration effect drops off very rapidly as the distance from the cold increases.

For the successful administration of local hypothermy metal applicators, preferably of silver or copper, are indicated as the best heat conductors. The applicators should fit the area accurately, for even a thin layer of air serves as an effective insulator, thus reducing the effectiveness of the treatment. They should be held in position firmly but without pressure, as pressure plus cold spells necrosis. The most satisfactory apparatus needs to be designed almost individually for the particular case. Blankets, hoods, boots, jackets, head-bands, and the like, of rubber tubing sewn between two thin layers of cloth, and thus serving as a closed circulatory system, give one more general flexibility in treatment. However, the insulating effect of the rubber, cloth and air must be taken into consideration and the circulating fluid must be considerably lower than that needed with the metal applicators. These various appliances can be attached to a special electrical refrigerator bedside unit * which circulates either water or a refrigerating solution such as Freone at a rate which assures a constant temperature at all times. The unit is applicable to the induction of either local or general hypothermy.

The most immediately practical use to which local hypothermy has been applied in other fields than cancer during the last few years has been presented by Allen and his co-workers in a series of papers² relating to the effect of variation in temperature upon circulatory disorders in general, and upon peripheral vascular disease in particular. In their most recently published paper³ they report 45 cases of vascular gangrene on whom 57 amputative operations were performed. In the series there was only one death attributed to operative mortality, and six other deaths occurring within a six-week postoperative period which were dependent upon fatal conditions antedating the operation. More than half the patients were diabetic, 13 were women, seven were negroes, the ages ranged from 49 to 85 years, two-thirds of them being over 65 years. The advantages of the procedure are the absence of pre- or postoperative pain, the prevention of immediate postoperative shock and the lack of postoperative complications, particularly infection, thrombosis and embolism. In addition the patients retain their appetites and spirits. These cases, climaxing years of work in a search for a method of controlling and treating diabetic gangrene promise to become a milestone in the history of traumatic surgery of the extremities. McElvenny⁴³ has reported a case in which the method was used to control infection in a bilateral traumatic amputation, and it is certain that many such reports will be forthcoming in the next few months. Blalock and Mason⁴⁴

* This apparatus may be obtained from the Therm-O-Rite Corporation of Buffalo, N. Y., who have cooperated in the development of satisfactory therapeutic equipment.

somewhat grudgingly confirm the physiological accuracy of Allen's studies in respect to the relationship of temperature reduction to a lowered incidence of shock

Aside from the surgical aspects of Allen's work, there are several other possible clinical applications of the use of hypothermy in the medical treatment of peripheral vascular disease. It is Allen's contention that with ischemia of an extremity due to occlusive vascular disease the metabolic requirements of the tissues are not met by the diminished blood flow. Therefore, the use of heat is definitely contraindicated, as increased temperature increases cellular metabolic demands and the ischemic blood supply becomes still further inadequate. By reducing the temperature of the extremity, cellular metabolism is reduced, the blood supply is adequate and gangrene is prevented. Theoretically, at least, if this is maintained over a long enough period, repair and revascularization might take place. Freeman,²⁶ in a recent communication, confirms these observations and recommends that the temperature of the air around an ischemic extremity be maintained at 30° to 34° C. Brooks and Duncan,¹¹ using a very accurate and elaborate technical method, showed that rats' tails would survive complete ischemia for a period of more than 96 hours at 1° C without the development of gangrene. Allen had previously shown^{2b} that "when the temperature can be maintained at about 2° C the limbs can survive asphyxia for a long period, the maximum of which has not been accurately established, but which is certainly more than 50 hours." From these observations it would seem that hypothermy is beginning to gain the recognition as a local therapeutic agent which it justly deserves.

GENERAL HYPOTHERMY

As a result of the regressive changes which Smith and Fay⁵⁰ observed in cancerous growths from the local application of cold, and the striking interference with normal cell growth and differentiation noted in preliminary laboratory studies with reduced temperatures, it was but a logical step to attempt to reproduce a comparable lowering of the whole body temperature in order to find out whether similar regression might occur in deep seated metastatic lesions. Hydrotherapy and antipyretic drugs have been used clinically throughout the centuries for reducing the body temperature in fever, but only to restore the tissues to normal physiological levels. Considerable literature has accumulated on the effects of lowering the temperature of experimental animals. Recently Woodruff⁷⁰ has reported that dogs would not survive blood temperature of 80° F for many hours. Simpson and Herring⁵⁸ and Troedsson,⁶⁵ however, have shown that in the cat, rabbit and even monkey (non-hibernating animals), a condition simulating hibernation can be induced by narcosis and a body temperature of 56° to 60° F attained and maintained for hours.

The question of nomenclature regarding the physiological state of these patients has been the occasion of considerable controversy. For want of a better term we originally suggested "hibernation" (always in quotes) as being useful descriptively. It still is. In dealing with the patient of today it seems preferable to speak a language which he understands. He is not familiar with the fundamental physiological differences of temperature control of the homeotherms and the poikilotherms. He speaks of "fever" treatment with almost colloquial familiarity—not of hyperthermia. Cold narcosis would mean nothing to him, and the same might be said of cryotherapy, crymotherapy and hypothermia.

Obviously, "hibernation" is a misnomer scientifically. We might point out that a somewhat similar state develops in certain poikilothermic animals and reptiles during the dry, summer months, which is termed "aestivation." Thus, it is not a question of external temperature alone, but apparently a protective mechanism designed to preserve the life of the animal through periods of inadequate food or water supply. As a preliminary to this change the animal usually builds up a supply of fat or, in the case of the cold-blood animal, of water. Hunger or thirst, as the case may be, coupled with temperature changes seem to be essential to the development of the hibernating stage. Chamberlain,⁷ for example, has remarked that he could induce hibernation in squirrels at any time of the year by starving them first for 24 to 48 hours and then putting them into a refrigerator. Without the initial hunger phase, however, he could not accomplish his objective.

The mechanism of hibernation is a complex one which has intrigued physiologists for centuries and which recently, perhaps in part stimulated by our studies, has been the subject of considerable investigation. Parker⁵¹ has shown that certain tissues in fish can absorb hormones, and suggests the possible analogy that the lipid tissues of the mammal may act in a similar way to inactivate normal metabolic activity. Sevringhaus^{56a} has suggested a similar possibility in respect to the storage of estrogenic substances by fat, as explaining the less spectacular results obtained in obese patients undergoing endocrine therapy. It is, of course, well known that the ordinary hibernating animals such as the hedgehog have certain special fatty organs, sometimes spoken of as hibernating glands, which store huge quantities of fat. This is also true of the bear, and a rather close analogy exists in the "hump" of the dromedary to the nutritional needs and the maintenance of water balance of the animal, although hibernation in the usual sense of the word does not occur. Similarly the steatopygy of the Hottentot may well have a similar functional purpose, as Wells⁶⁰ has pointed out.

Akiyama¹ found that squirrels in hibernation were protected from what would otherwise be a fatal inoculation of a tumor producing virus. Tainter,⁶¹ at Stanford, noted that animals failed to exhibit the usual toxic reactions to drugs like dinitrophenol if they were maintained at temperatures of 33° to 42° F. Suomalainen,⁶⁰ in Helsinki, found that the injection of

* Personal communication.

magnesium chloride would hasten the normal hibernation of animals in the fall, and that conversely calcium chloride prevented the development of the hibernating stage or brought the animals rapidly out of hibernation. He likewise noted low blood sugar and low adrenalin content of the blood in his animals. Pfeiffer,⁵² in Chicago, working with the ground squirrel confirmed the work of both Suomalamen and Tainter. Even Harvey Cushing¹⁹ some years ago suggested the probable importance of the pituitary in hibernation, because of its fairly well accepted relationship in water metabolism, and because he noted definite changes in the cells of such animals during hibernation.

Herrmann³⁴ and Barbour⁶ in particular have stressed the physiological differences of thalamic temperature regulation in true hibernating animals and in the state which is induced by light narcosis and the reduction of body temperature in homeothermic mammals. They review certain of the theories regarding the nature of hibernation which have been propounded in the past century since Marshall Hall's³¹ concept that hibernation was a form of sleep differing from normal sleep only in degree, and in altering the irritability of the heart through diminution of respiration and a consequent change in the chemistry of the blood. Herrmann^{34a} further studied the effect of small doses of sedative and antipyretic drugs in animals exposed to cold and noted that the toxicity of morphine, paraldehyde and certain of the barbiturates was greatly increased at low environmental temperatures, and that they caused a transient further drop in the body temperature. Magnesium chloride in non-depressant doses similarly has a hypothermic effect. It is interesting to note that aspirin produces no temperature drop except in the presence of actual fever.

Rosenthal⁵¹ in studying picrotoxin and aconitine comes to the conclusion that there is a true "cooling" center located in the diencephalon and closely related to the centers controlling the parasympathetic system. No one man could possibly qualify nor does time permit digging into the fascinating but vast and complex field of temperature regulation, with its many ramifications into the related sciences—physics, engineering, chemistry, physiology and general biology. The names of Barbour of Yale, Bazett of Pennsylvania, Benedict of the Carnegie Foundation, DuBois of the Russell Sage Institute, and a host of others need only be mentioned as leaders in the medical aspects of this problem, to whose publications the reader is referred.

Other things being equal, in generalized hypothermy patients are made to all intents and purposes poikilothermic. It is true that this state is difficult, if not impossible, to attain in all patients unless preliminary sedation is used. However, small, non-depressant doses of drugs such as "Evipal" which act only briefly serve admirably to overcome the ordinary reflex reactions of shivering which occur chiefly while the temperature is falling to about 92° or 93° F. It is difficult for us to conceive of any prolonged narcotic effect of such sedation, as Herrmann³⁴ and others have intimated. Talbott⁵³ expresses the same point of view when he states: "Within an hour,

the anesthetic effect of the Evipal has for the most part worn off, and simultaneously the body temperature decreases. The anesthetic property of the cold usually obviates the necessity of further intravenous anesthesia or sedative."

If the effects of lowering the temperature inversely follow van't Hoff's law, then a reduction of body temperature of 10° to 12° C from 37.5° C to 23° C or 24° C should lower the rate of chemical and physical processes, viz., metabolism, to about half the former level. That figures approaching this theoretical level actually are attained can be shown by various physiological phenomena which occur while the patient is in that "profound oblivion midway between sleep and death" as Nuzie⁴⁸ expresses it in describing some carefully controlled experiments on dogs, in which body temperature was reduced to 79.5° F in the course of about six hours' exposure to an environmental temperature of 44° F. Basal metabolism in our series was reduced from 20 to 50 per cent although, as Talbott points out, part of this reduction may be attributable to intermittent sedation during treatment.

Many interesting physiological phenomena may be observed in the patient who is subjected to generalized hypothermy. Not the least interesting and important of these relate to the cardiovascular system. The heart rate tends to become slowed, although rarely below 50 beats per minute. The circulation time is prolonged, two or three times above normal. Blood pressure and the peripheral pulse may disappear entirely for hours at a time, constriction or collapse of the peripheral veins occurs, often rendering venipuncture impossible, but neither we nor others have ever observed actual thrombosis. Blood volume is presumably decreased as the result of a true anhydemia as shown experimentally by Harkins,³² by Barbour,⁶ and by DuBois,²¹ the fluid being withdrawn into the interstitial spaces and even accumulating intracellularly as a mechanism designed to retain heat and thus reduce radiation. The volume output of the heart per minute is reduced. Evidence of this is seen in electrocardiograms in which the T-wave tends to become inverted or abnormal and in which there is a prolongation of the electrical systole. As Kossman²⁰ summarizes his experiences, decreased temperature is accompanied by a slowing of the pulse rate, a tendency towards lowering of the blood pressure, marked arterial, arteriolar and venous constriction, abnormality of the T-wave, the occurrence of auricular fibrillation above 85° F and prolongation of electrical systole principally due apparently to a delay of the recovery process not related to alteration in the serum calcium. On the basis of observations of this character, and because of the occurrence of circulatory collapse and death either during the period of return of the temperature to normal or within a 24-hour period subsequently, in three or four instances, we had become somewhat concerned that myocardial degeneration was taking place because of anoxia resulting from the decreased cardiac output. It was not until an analysis of an equal number of terminal cases of malignancy that did not undergo refrigeration showed a slightly higher incidence of such circulatory failure and myocardial change

that we became convinced refrigeration was not in itself a serious risk to the average patient. From the practical standpoint of physiology it seems better to us for the patient to come out of his refrigeration state slowly, so that the load on his heart will not become suddenly too great. Likewise, it seems reasonable to give intravenous fluid during this period in sufficient amounts to compensate for the relaxation of the peripheral circulation which obviously takes place.

So far as the blood itself is concerned, we are likely to have an early hemoconcentration with a rise of the red cell count of anywhere from a quarter of a million to a million cells. There is usually a disproportionate leukocytosis up to as high as 15,000 or 20,000 and in occasional cases even to 40,000 or 50,000 cells. This rise is largely of the neutrophils and disappears within a few hours after the temperature returns to normal. In cases that have been given several periods of refrigeration there is a tendency towards the development of a mild anemia, the result of disturbed maturation of the red cells from the cold. Likewise the leukocytosis is likely to be less marked in the fourth, fifth or subsequent refrigeration periods.

In a condition in which such profound changes occur clinically it is surprising that so little is found of an abnormal nature in the blood chemistry. There is no apparent significant alteration of the plasma proteins or A/G ratio. In our experience^{59a} there has been no retention of nitrogen. In fact, in the majority of the cases studied there has been a definite tendency for the urea and non-protein nitrogen to fall even below the low side of normal. Vaughn⁶⁷ reported similar findings. On the other hand, Dill and Forbes²⁰ in their one fatal case noted such nitrogenous retention terminally. Blood sugar tended to drop, the average figure being between 80 and 90 mg, suggesting a resting state of the liver perhaps. Cholesterol and cholesterol esters appeared unchanged. No significant alteration in the calcium-phosphorus balance was noted. More attention should be paid to the other salts, especially potassium and magnesium, in subsequent studies. Carbon dioxide measurements were mostly within normal limits, although a few cases showed a little tendency towards the development of a very mild relative acidosis, which could be controlled readily by administration of glucose and fluids by mouth.

No impairment of renal function is apparent. If fluids are given, they are excreted with very little loss through respiration or the skin. Urinalysis has been regularly negative. Postmortem examination has not revealed any acute or other changes possibly attributable to refrigeration.

In general we have found it more satisfactory to withhold food during the refrigeration period except for small amounts of fluid and glucose, because the presence of food tends to activate the whole physiological mechanism and it is more difficult to maintain the temperature level desired. On the other hand the patient can be aroused, will swallow fluids and soft solids, although in many cases the swallowing reflex is poorly preserved.

Digestion seems entirely normal, although defecation during refrigeration is only rarely observed

The one serious complication which we have seen in general refrigeration relates to the pancreas. Every now and then a patient develops a moderately severe acute pancreatitis. We have seen five such cases, and careful histologic study of all generalized hypothermy cases who have come to autopsy in the series reveals an incidence of minor inflammatory and degenerative changes of the pancreas in nearly 10 per cent. Daily blood amylase determinations during the refrigeration period should give adequate warning of impending disaster, and the patient's temperature should be restored to normal promptly to avert any serious complication. We have not yet been able to determine any particular reason for this discriminatory selectivity of the pancreas for trouble. Possibly its enzyme activity is not proportionally decreased as much as is the tissue resistance through relative anoxia from a diminished blood flow.

Curiously enough the respiratory rate is not usually altered much. The tendency is towards a gradual drop in rate to perhaps 12 or 14. In occasional cases it may fall to 8 or 10, and occasionally a rise to 28 or 30 may take place. The excursion is definitely reduced, so that breathing is "shallow" and ventilation correspondingly lowered. This apparently is a purely compensatory mechanism to match the reduced blood flow, for the color of these patients is essentially normal, without cyanosis. Because of the low temperature which is bacteriostatic for most of the ordinary upper respiratory bacterial flora, the development of pneumonia, although obviously presenting a certain risk, is no more likely to occur in a group of patients of this type than in the non-refrigerated cases. A terminal, patchy bronchopneumonia, which they felt was of no great importance, has been reported by Talbott⁶⁴ in the one fatal case in their series.

Subjectively, the mind is a complete blank from the onset of the induction period, except occasionally for a vague recollection of feeling cold as the temperature returns to normal through the "shivering zone" (92° to 97°). Exhaustive studies of the brain pathologically on more than 50 cases coming to autopsy following as many as seven and eight inductions have failed to reveal any demonstrable changes either grossly or microscopically.^{55b} We had thought that with a slowed circulation we might encounter degenerative changes from cerebral anoxia, but there is absolutely no evidence, clinically or pathologically, of potential significance in so far as the application of general refrigeration in functional disorders of the brain is concerned. In this connection, it is of interest to note that the procedure has been employed by Talbott and his associates⁶³ in a series of schizophrenic patients with extremely gratifying results. It is of interest to us not only from the neurologic and psychiatric viewpoints, but because it represents what might be considered a normal control experiment for us in our work with terminal cancer cases.

Talbott⁶³ found that generalized hypothermia in schizophrenic patients under 30 years of age who had been sick for less than three years, with one exception, resulted in striking improvement which had been continuous for more than six months. In the older chronic cases no prolonged alteration in their mental symptoms occurred. Most of these patients had been treated previously with insulin or metrazol, or both, without benefit. He concludes that "with such promising results continued efforts in the use of hypothermy are thoroughly justified." In the one fatal case he states that there are three major trends in the acid-base balance of patients during hypothermia, i.e., hemoconcentration, acidosis, and retention of substances usually excreted by the kidney. This is accompanied by an alteration in the Ca/K ratio of the tissues, with Ca somewhat decreased and the K correspondingly increased. These various clinico-pathologic features are separately discussed in detail by Dill and Forbes²⁰. They further conclude that prolonged hypothermia is without serious morphologic effect on the tissues.

SUMMARY

From these somewhat disjointed comments regarding the biologic effects of cold on cell growth and differentiation and on mammalian physiology, it is hoped that the concept has emerged of the potential value of hypothermy in medical therapeutics. In spite of centuries of almost subconscious recognition of the usefulness of cold in the treatment of pain and fever, perhaps because of its very simplicity, its more extended use has only just begun to be explored. The brilliant work of Allen,² Crossman³ and their associates in the peripheral vascular diseases and their associated surgery has pointed the way towards a new era for the diabetic and for military and civilian traumatic injuries of the extremities. The pioneering of Talbott⁶² with generalized hypothermia in schizophrenia likewise opens the entire field of central nervous disorders to similar investigation. In our own work in malignant disease we believe we have conclusively shown the value of hypothermy in both localized and generalized application as an adjunct to other methods of treatment, and especially in the management of the terminal stages of the disease. Its value in the control of pain is often truly phenomenal and for this reason alone the method should be employed widely in a variety of pain problems. Its use in the treatment of narcotism seems well substantiated. Its value in the control of infections locally cannot be over-emphasized. The clinical exploration of its value in a host of other pathologic states seems fully justified and urgently indicated. We must reexamine our present concepts of physiology in the light of these new temperature levels attained, and successfully maintained by man. Perhaps it is not too much to hope that as our knowledge grows, it may be possible clinically to reach safely the "critical" levels of tumor cell growth which our tissue cultures suggest may well be destructive to cancer cells, and thus add an-

other truly effective weapon to the war against malignant disease. The evaluation of hypothermy as a therapeutic agent can only be attained by the combined efforts of the clinician and the laboratory man over a long enough period of time to discover its limitations as well as its usefulness. During this experimental period it is probably just as well that its more intensive application be limited to the larger institutions which have the facilities and personnel to carry out such investigative problems. In its present stage of development, like any other major therapeutic procedure—surgery, hyperthermia, even serum and chemotherapy—it is not without certain dangers, which must be recognized and methods designed to counteract them. These difficulties do not seem in the least insurmountable.

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THE SYSTOLIC MURMUR*

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THE systolic murmur is not an uncommon finding in routine examinations. Reid and Fahr have reported an incidence of as high as 20 and 35 per cent in normal youthful patients. The pendulum of opinion regarding the importance of these systolic murmurs has swung over a wide arc in the last century, from the extreme importance first attached to any murmur heard through the stethoscope to the view that murmurs were of no importance at all, and recently back again to viewing the systolic murmur with extreme suspicion. Mackenzie,¹ in his long continued follow-up studies, states that he has seen many individuals, with very loud rasping systolic murmurs for 30 years and with a rheumatic fever history, who never suffered from heart failure, and he states "where there are functional murmurs, the leak, if this be present causing them, is slight and never such as to embarrass the auricles in their work apart from cases where there is grave damage done to the heart muscle." He also says "the estimation of the sign of functional murmurs is not based on the murmur itself but on the functional efficiency of the heart and on the presence or absence of other signs of cardiac affections (size, rate, and rhythm)." From this point of view, there have been published recently many papers giving great importance to the systolic murmur. Thus Levine² claims "systolic murmurs do occur, but are not common in normal individuals" and, after classifying these murmurs according to loudness from class one to class six, states "the loud ones are always associated with some form of cardiovascular disease." He includes, in a series of 1000 cases, all systolic murmurs even if complicated by conditions which would, as Blumgart³ pointed out, cause a murmur because of the increase of the velocity of the blood stream, such as a severe anemia, hypertension, and hyperthyroidism. On the other hand, R C Cabot⁴ pointed out that without other signs of cardiac disease the systolic murmurs are of no importance as evidence of valve lesions and claims "a diagnosis of mitral regurgitation without stenosis is never justified." Other investigators^{5, 6, 7, 8} have reported varying views with reference to the importance attached to this condition.

A very confusing factor is the reliance to be placed on insurance statistics, which have led most insurance companies to conclude that there is no such thing as a functional murmur and on that basis to rate up heavily or reject for life insurance an applicant with a murmur. F H McCrudden,⁹ in a recent article, states that there is a definite decrease in life expectancy with apical systolic murmurs. In a recent review of 2,100,000 insurance

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cases from 1909 to 1927 inclusive, the conclusion is reached that there is a tremendous increase in the mortality rate of all cases with a systolic murmur except those in which the murmur is at the pulmonic area, soft, inconstant, and not transmitted

Fineberg and Steuer¹⁰ analyzed 100 cases presenting a systolic apical murmur which they had observed over a period of years. They concluded that in youngsters with a systolic murmur and a history of rheumatic fever or chorea there is a 50 per cent chance for the development of mitral stenosis, aortic regurgitation or both, that mitral stenosis or aortic regurgitation appeared on the average three to four years after the first observation, and that in only eight instances did the murmur disappear. Recently, however, the same authors reported the observation for over 10 years of 35 of the original 100 patients without the discovery of any new cases of mitral stenosis or aortic regurgitation.

In the series of cases we are now reporting we have taken only those in whom there is no associated disease which might have caused the murmur and only those in whom careful physical examination, vital capacity, electrocardiographic, orthodiagraphic, and laboratory studies convinced us that the heart was normal in spite of the presence of a systolic murmur. In this series were also included those cases with a history of rheumatic fever or chorea. In concluding that there was a systolic murmur present, we defined the systolic murmur, as did Freeman and Levine,¹¹ as a "distinct bruit that is heard definitely following the first sound and extending appreciably into systole." We did not group them according to loudness, but in this series there were murmurs of varying intensity. In other words, this is a study of the pure systolic murmur as such and as evidence of an embarrasing valve lesion. Approximately 23 per cent of the cases referred to the Cardiac Clinic for cardiac examination were called normal and about 25 per cent of these normal cases had a systolic murmur. We were not interested in the significance of this systolic murmur as regards pathologic lesions of other organs. We have studied a group of 100 cases (not consecutive) with systolic murmurs over a period of from four to 16 years, ranging in age from 12 to 71 years. In the first 100 consecutive cases, we were able to get a return of 72 and were unable to trace the remaining 28. Of these 28 whom we could not trace, the Minnesota State Board of Health reports that there have been five deaths with two dying of pneumonia, one postoperatively, one of ruptured appendix, and one of melanotic carcinoma.

Of the 100 cases (not consecutive), 28 had a definite history of from one to three attacks of rheumatic fever or chorea occurring from three to 27 years before the first examination by us. A great majority of them had been restricted in activity before coming to the clinic and many had been given cardiac medications. The average follow-up period was about seven years. The murmur was located at the apex in 44 cases and at the base or sternum in the remainder. Electrocardiograms were taken on all cases and were negative. Every case also had an orthodiagram and esophagogram.

Bardeen,¹² checking the relation between heart volume, transverse diameter and area, found that their interrelation was sufficiently constant to justify the use of transverse diameter and area as indicative of heart volume. In determining the heart size in this series the measurements of the heart were limited for practical purposes to the transverse because, as pointed out, measurement of area frequently involves, besides the experimental error in obtaining heart outline, a further error in measuring it. Variations in the position of the heart were corrected by correlation with body height, weight, and age, and by comparison with the predicted transverse normal as obtained by the formula of Hodges and Eyster,⁹ which can predict that diameter with an error of less than five mm (the transverse diameter of the heart = $+0.1094 \times \text{age} + 0.8179 \times \text{weight} - 0.1941 \times \text{height}$)

Assuming that after a follow-up period of this length of time, the heart, if embarrassed by a valve defect of any consequence, should certainly show some signs of cardiac disease besides the systolic murmur and an increase in heart size of measurable degree, the findings of the last examination were compared with those of the first. In these 100 cases we found, after an average period of seven years, 96 showing no significant changes in electrocardiograms, orthodiagram, vital capacity, esophagogram, or physical findings. The standard deviation in these 96 cases seen in a large cardiac clinic in the orthodiagram studies was only 5.4 mm. An increase beyond the predicted transverse normal, as determined by the formula of Hodges and Eyster,⁹ as well as any marked increase in this diameter beyond the first measurement, was considered abnormal. It bespeaks the extreme accuracy of carefully done orthodiagraphy that no more care was taken in the fluoroscopic examination of this group of patients than of those routinely examined in the cardiac clinic. After this follow-up period of seven years, we have the following four cases who, at the last examination, had developed definite heart abnormalities besides the systolic murmur and now showed definite cardiac findings.

CASE REPORTS

Case 1 This woman was first seen in 1933, was 20 years old, 5 ft 5½ in tall, and weighed 114 lbs. Family history was negative. She gave no cardiac symptoms, but there was a history of chorea at the age of 11. The only cardiac finding was a systolic murmur at the base, moderately loud, not transmitted, and not affected by breathing or exercise. No diastolic murmur was heard. Vital capacity, electrocardiogram, and esophagogram were normal. Orthodiagram showed the heart to be normal in shape with a transverse measurement of 9.7 centimeters. When examined in 1938 this patient still had no symptoms. The systolic murmur was then heard at the apex and was transmitted to the axilla. There was still no diastolic murmur. Vital capacity was still normal but electrocardiogram now showed a tendency to right preponderance and the heart had increased 3.1 centimeters in transverse diameter to 12.8 centimeters. The transverse thoracic measurement was 21.8 centimeters. The esophagogram was still negative. We now consider this a case of possible pure mitral regurgitation.

Case 2 This case is that of a young girl aged 15, 5 ft 6 in tall, weight 115 lbs who was first seen in 1932 with no cardiac symptoms, a negative family history, and a

negative history of rheumatic fever. The only finding was a systolic murmur at the apex, constant but not transmitted. There was no diastolic murmur heard. The vital capacity was normal. The electrocardiogram showed a tendency to left preponderance but was otherwise negative. The orthodiagram revealed a normal shaped heart though with a slight fullness of the conus area which is sometimes seen in a drop type of heart. The esophagogram was negative. The transverse diameter was 11.9 centimeters. When seen again, in 1934, the findings were the same and there were no cardiac symptoms. The electrocardiogram, however, now showed a tendency to right preponderance, and the orthodiagram revealed a transverse heart diameter of 12.6 centimeters. The patient was seen again in 1938 and had shown a further increase of the transverse diameter to 13.3 centimeters, with a transverse thoracic measurement of 23 centimeters or a total increase in six years of 1.4 centimeters. The esophagogram has been negative at all times and no diastolic murmur has ever been heard. We now believe this to be a case of possible mitral regurgitation.

Case 3 This patient was a man aged 25, 5 ft 8¼ in tall, weight 173 lbs, first seen in 1931. He had a negative family history, but gave a history of rheumatic fever at the age of 18. The only cardiac finding, when he was first seen, was a systolic murmur at the base, not constant and not transmitted. Electrocardiogram, vital capacity, orthodiagram, and esophagogram were normal. The transverse diameter of the heart was 12.5 centimeters and the transverse thoracic diameter 25.5 centimeters. Five years after this examination this patient had another attack of rheumatic fever. When reexamined in 1938, this man had developed not only a systolic murmur at the apex but a typical mitral-diastolic murmur. He still had no cardiac symptoms. His vital capacity was still normal, but his esophagogram was now positive to the right and to the posterior. The transverse diameter of the heart had increased 1.4 centimeters to 13.9 centimeters. He had a definite conus bulge with a typical mitral shaped heart. We believe that the last attack of rheumatic fever, in 1936, damaged the mitral valves.

Case 4 The fourth patient was a woman aged 41, 5 ft 3¾ in tall, weight 153 lbs, first seen in 1931. She gave a negative family history, negative history of rheumatic fever, and had no cardiac symptoms. The only cardiac finding was a loud constant systolic murmur at pulmonic area. Vital capacity was normal, as were orthodiagram and electrocardiogram. The orthodiagram revealed a normal shaped heart with a transverse diameter of 11.75 centimeters with a transverse thoracic diameter of 24 centimeters. When this patient was examined in 1938 she still had no cardiac complaints. The vital capacity was still normal and the systolic murmur was the same, but on orthodiagram the transverse diameter of the heart was definitely increased by 1.4 centimeters to 13.1 centimeters. Electrocardiogram now showed a flat T₂ and a negative T₃. Her blood pressure had remained 130 mm Hg systolic and 86 mm diastolic. We now believe that this patient has developed coronary disease.

It would be reasonable to assume that, even with a rheumatic history, if these cases showing systolic murmurs had a valve lesion which would affect their heart efficiency to any appreciable degree, some finding other than the heart murmur should be elicited in the period of time covered. Beyond the cases stated this was not true. In one case coronary disease developed, and we believe only two cases really had a mitral insufficiency at the time of first diagnosis, as the heart in the other case was probably damaged by a later attack of rheumatic fever. It is also interesting to note that the hearts which later showed cardiac findings other than the systolic murmur were followed for a period of six and one-fourth years and showed very marked increases in heart size whereas the others did not. It is important

to note that of the four cases reviewed which developed demonstrable heart lesions in addition to the murmur only two had a history of rheumatic fever, and that these cases which did not develop definite signs of cardiac pathologic lesions did not have a history of rheumatic fever within a period of at least three years prior to the first examination or thereafter. The only case in which a diastolic murmur could be heard at the second examination was one in which the patient had had a new attack of rheumatic fever two years before the last examination.

CONCLUSION

We did not try to diagnose conditions in organs other than the heart by the systolic murmur, but in spite of the fact that these cases of systolic murmur were not consecutive, we believe a vast majority of them were normal hearts as far as functional capacity is concerned and that "if we find in a heart of normal size and rhythm a systolic murmur with absence of any sign that would indicate that it is definitely organic in origin and with a good functioning organ, then we may conclude that the heart is perfectly normal. If there be evidence of weakness or other signs of abnormal conditions present, then the opinion should be based on these other signs and not the murmur."

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POLLEN IN OIL: A PRELIMINARY REPORT ON A NEW, SLOWLY ABSORBED MEDIUM FOR USE IN HAY FEVER TREATMENT*

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DUNBAR, in 1905, was the first to attempt pollen desensitization against hay fever. He injected horses with crude pollen, then bled the animals and used the serum on hay fever patients. It is very obvious that this treatment was unsuccessful because of horse serum reactions, and the method soon fell into bad repute.

Noon, in 1911, was the first to place desensitization on a scientific basis by preparing an aqueous extract of timothy pollen. This work was further elaborated by Freeman, Koessler, Scheppegegrell and Clowes. Glycero-saline extracts are still claimed to be the most stable, but when used in 50 per cent concentration of glycerine and injections of 3 per cent pollen are given to patients, they are very irritating and painful. This has been a serious drawback to its use in 3 per cent concentration.

Extracts of pollen in 5 per cent glucose have overcome this objectionable feature, but like all aqueous extracts the greatest obstacle is the rapidity of absorption with its consequent local and general reactions. Spain and Sammis, in 1935, used ultrafiltered extracts and reported more successful desensitization.

Harrison, in 1934, studied the effect of alum precipitated pollen extracts on guinea pigs. He felt that the addition of alum might slow down absorption and allow for the use of higher concentrations of pollen.

Caulfield, Brown and Waters added alum as an adjuvant in sensitizing guinea pigs to ragweed pollen. They were successful and reported that sensitization was produced more readily by this method.

Keeney, Pierce and Gay were the first to prepare epinephrine in oil. The epinephrine was suspended in sterile peanut oil. This has been a great advance in the treatment of asthma because of the slow absorption and consequent sustained action of the epinephrine.

For a number of years poison ivy and oak extracts in oil have been used both prophylactically and therapeutically with excellent results for ivy and oak dermatitis.

In view of these attempts to use oil extracts it occurred to one of us (S J T) that if pollen could be prepared in oil such a mixture could be used to great advantage in the treatment of pollinosis.

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The technical preparation of this mixture was undertaken with the assistance of Dr S O Levinson of the Serum Center of Michael Reese Hospital

It is generally known that many patients will have both severe local and constitutional reactions from the usual aqueous pollen mixtures. The large number of injections required both preseasonally and perennially often are objectionable to many patients. The patient who presents himself for treatment during the pollen season has always been a problem. The rapid method of desensitization with the resulting rapid absorption occurring with aqueous solutions has been a source of severe reactions and a serious drawback to that method of therapy.

TECHNIC OF EXTRACTION OF POLLEN IN OIL

An aqueous 3 per cent pollen extract solution was frozen in a carbon dioxide, carbon tetrachloride mixture and evaporated to dryness in vacuo. The residue was then redissolved in sterile sesame oil. As the solubility of the residue is slight, it is necessary to leave it in contact with the sesame oil at room temperature for six days. Aerobic and anaerobic cultures of the sesame oil-pollen extract mixture showed no bacteriologic growth after seven days' incubation at 37° C.

There have been no reports of sensitization to sesame oil. Sensitization to peanut oil and poppy seed oil have been frequently reported. Sesame oil can be easily sterilized in an autoclave for 15 minutes at 15 pounds of pressure. It has a low specific gravity and runs easily through a 27 gauge needle.

Intradermal tests were made on 200 ragweed sensitive patients and delayed positive reactions resulted in all of them. Reactions consisted of erythema and itching coming on 30 minutes after the intradermal test. Small pseudopods were present in some patients. Control tests with sesame oil were negative. By this method it was possible to produce a 20 per cent pollen mixture, and intradermal tests made with this concentration merely resulted in a larger area of erythema and more marked itching coming on about 30 minutes after the test. In a few patients itching persisted for 24 hours following the test but the erythema persisted for one hour. Further observation revealed that, after a quiescent period of one week, there is a reappearance of the reaction consisting of a raised red papule with itching, again indicating the slowness of absorption. No constitutional or marked local reactions occurred with the 20 per cent pollen in oil mixture in any patient. Dry pollen is suspended with difficulty in any oil, however, after lyophilization the active principle is not altered in any way and is more easily suspended in oil. It can be kept at room temperature without deterioration.

CONCLUSIONS

- 1 The active principle is present in these oil extracts as evidenced by the local reactions produced in sensitive individuals.
- 2 A slower rate of absorption is demonstrated, with less likelihood of severe local and systemic reactions.

3 Higher concentrations of pollen extract are possible with pollen in oil and, therefore, patients can be given a single large dose with no danger of constitutional reactions

4 These extracts do not deteriorate at room temperature and need not be refrigerated

5 We are reporting this preliminary work because we feel that pollen in oil has such tremendous possibilities, not heretofore obtainable with aqueous extracts

A report on its use in patients with hay fever symptoms will be made at a later date

Note Since this article was written in June 1941, the lyophilized pollen and the sesame oil have been homogenized rather rapidly by the use of an electric homogenizer. The active extract does not separate out, on standing in this oil mixture, and a perfect homogenized mixture results

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SOME PHYSIOLOGICAL OBSERVATIONS ON THE CIRCULATION DURING RECOVERY FROM VITAMIN B₁ DEFICIENCY *

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OBSERVATIONS on the cardiovascular disturbances accompanying vitamin B₁ deficiency in man have accumulated rapidly during the past decade. Aalsmeer and Wenckebach¹ and Keefer⁷ described the cardiac form of beriberi occurring in the Orient. Scott and Herrmann¹² found similar cases of cardiac failure among the rice cultivators of Louisiana who developed the "maladie des jambes" each autumn when the diet consisted of polished rice and bacon grease.

Minot, Strauss and Cobb⁹ recognized the importance of nutritional deficiency and especially deficiency of vitamin B₁ in the etiology of "alcoholic" polyneuritis and compared this condition to beriberi. A few years later Weiss and Wilkins¹⁷ reported a number of cases of cardiac failure associated with nutritional deficiency, described the syndrome, and called attention to its relative prevalence in the western countries among those addicted to alcohol. Since then, there have been numerous reports, some on isolated cases, others on series of cases, all of which have been comprehensively reviewed by Weiss in a recent article¹⁶. In this he sums up the evidence in favor of a causative relation between thiamin deficiency and the cardiovascular dysfunction of beriberi.

Of the total number of contributions to this subject during the past 12 years, only a small fraction have been concerned with this syndrome from the standpoint of circulatory dynamics. Studies made by Weiss and Wilkins¹⁷ demonstrated that in heart failure from beriberi the circulation time is *decreased*, an observation which points to an increase in the velocity of blood flow, and that the arteriovenous oxygen difference, as measured by blood samples taken simultaneously from femoral artery and vein, is diminished, which suggests an increase in the volume of flow. The venous pressure was elevated in some of their patients. Weiss and Wilkins concluded from these and other studies that the circulatory disturbance accompanying beriberi is caused in the main by a combination of arteriolar dilatation and myocardial failure.

Prior to the work of these authors, Hayasaka and Inawashiro⁵ made studies on the minute volume of patients with beriberi using the original ethyl iodide method of Henderson and Haggard⁶. In the light of Starr and Gamble's¹³ later work, their figures are probably too high, but they may be

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relatively significant, and the conclusion that the cardiac output in beriberi is increased is strongly suggested by the figures they present. These investigators also believed that relaxation of the peripheral vessels was the chief cause of the increased minute volume. These physiological observations of Hayasaka and Inawashiro and of Weiss and Wilkins indicate that circulatory failure in beriberi is somewhat different in mechanics from that caused by the more common etiologic factors such as hypertension, rheumatic valvular disease and coronary artery disease. Moreover, the disordered functions leading to congestive heart failure in beriberi are more nearly reversible than those usually present in other forms of heart disease.

The present paper reports further measurements of the circulation in vitamin B₁ deficiency. It is based on observations of two patients with such deficiency, carried out during their recovery from congestive cardiac failure. The observations include repeated determinations of the cardiac output, arterial and venous pressures, circulation time, and oxygen consumption. In one patient several determinations of the blood volume were made. All determinations were made under standard basal conditions. Oxygen consumption was measured with the Tissot spirometer. The cardiac output was calculated by means of the acetylene method of Grollman³ using the three sample procedure suggested by Grollman, Friedman, Clark and Harrison⁴. The venous pressure was measured by the direct method of Lyons, Kennedy and Burwell⁵. The circulation time was determined by the "Decholin" method of Winternitz et al.¹⁸. The blood volume was measured by the method of Gibson and Evans.²

On one patient (J. L.) venous pressure, circulation time and vital capacity measurements were made on the day of admission before any specific therapy had been started. Thiamin was first given that evening, and on the following morning the blood volume and oxygen consumption were determined. On the second day after therapy was started the first cardiac output determination was carried out. On the other patient (R. J.) thiamin was started the day before admission and was continued without interruption until recovery was practically complete. The initial venous pressure reading was taken on the second hospital day, and the vital capacity and circulation time were measured on the following day. On the fifth hospital day the first cardiac output was determined.

It should be emphasized that these studies in no way represent the complete picture of the circulatory changes in B₁ deficiency. Because of technical difficulties and the serious condition of the patients, it was not possible to carry out all of the observations until after B₁ therapy had been instituted. Moreover, recent animal experiments indicate that vitamin B₁ deficiency is a relative state: an active animal may be in deficiency on a given vitamin intake whereas at rest with the same intake, adequate vitamin B₁ may be present to satisfy the demands. Hence although no additional vitamin has been given, the animal may no longer be deficient, in fact may be in a state of repair. Both these patients had been at rest in bed for several days pre-

ceding our studies For this reason, it is impossible to judge the exact state of deficiency in these two patients at the time the studies were instituted However, we believe that our observations are of interest in throwing some light on the problem of B₁ deficiency and present them here with the reservations mentioned above

CASE REPORTS

Case 1 J L, a 32-year-old unemployed married male, was admitted to the Peter Bent Brigham Hospital on June 6, 1940, with the complaint of puffiness of the face and swelling of the ankles For many years the patient had indulged in week-end spree During the past year the alcoholic intake had gradually increased up to two or three pints of wine and a quart of ale daily When financial straits prevented the purchase of these beverages, rubbing alcohol and other cheap substitutes were used About six months before admission he began to feel "rum sick" in the morning His appetite became poor, and frequently he ate but one meal a day Three or four months prior to entry it was noticed by the patient and others that his face looked puffy, and a month or so later he first noticed swelling of his legs At the same time he experienced tenderness in the calves of his legs and the soles of his feet on walking One month before admission he noticed shortness of breath on walking several blocks Two weeks before entry he developed red scaling lesions on the dorsal surface of both hands At this time his face and eyes were very puffy, there was marked increase in ankle edema, and he was unable to walk across the street because of dyspnea

His only illness in the past had been one attack of what was said to be rheumatic fever at the age of 10

Physical examination at the time of admission revealed an irritable, confused, puffy-faced male with strong alcoholic odor on the breath The rectal temperature was 98° F, the pulse was 120, and the respirations were 24 The skin was warm and moist Over the dorsal surfaces of both hands were erythematous, pigmented scaly lesions and similar lesions were present in the suprapubic region extending almost to the umbilicus The pupils were dilated and reacted sluggishly to light The tongue was large and thick but not abnormally red or smooth There was no cyanosis and no distention of the neck veins The cardiac dullness was enlarged to percussion and measured 11 cm to the left of the midsternal line in the fifth interspace and 3 cm to the right in the fourth interspace The rhythm was regular The heart sounds had a tic-tac quality, and at the apex a short, blowing murmur was present late in systole The blood pressure measured 128 mm of mercury systolic and 84 mm of mercury diastolic The lungs were clear of râles The liver was felt 4 cm below the right costal margin in the midclavicular line Edema of the ankles, legs and sacrum was present The positive findings on neurological examination included increased deep reflexes, marked sensitivity of the soles of the feet, tenderness of the calf muscles and coarse tremor of tongue, hands and feet There were no delusional trends or hallucinations at the time of admission

At the time of admission the red blood cells numbered 3,520,000, the white blood cells 7,800 The hemoglobin was 78 per cent by the Sahli method The urine had a specific gravity of 1.008, it contained no albumin or abnormal sediment Wassermann and Hinton reactions of the blood serum were negative The blood non-protein nitrogen, sugar and icterus index were normal The serum albumin and globulin in grams per 100 cc were 4.0 and 2.8 respectively The serum ascorbic acid was 0.1 mg per 100 cc (The normal range in this laboratory is from 0.4 to 1.5 mg per 100 cc) A roentgenogram of the chest on the day following admission was interpreted as showing enlargement of the heart, chiefly to the left, and a marked increase in the lung markings Fluoroscopy showed a heart beat of good amplitude Electrocardiogram showed normal complexes and left ventricular preponderance

Therapy with thiamin chloride and nicotinic acid was started about 24 hours after admission. Recovery from the state of obvious congestive heart failure present on admission took place rapidly. On the fourth day of hospital stay the pitting edema of the legs and ankles had disappeared, although some puffiness about the eyes persisted. At this time the systolic murmur had also disappeared. The leg tenderness, unsteadiness of gait and tremor improved more slowly, but the patient was able to be up in a chair on the ninth day in the hospital. At this time the lesions of the hand had entirely cleared up. His weight decreased from 67 kg on admission to 57 kg three weeks later on the day before discharge, and during this time his appetite and food intake increased greatly. Associated with the loss of weight there was a progressive rise in the red blood cell count and hemoglobin content toward normal values. Serial roentgenograms of the heart demonstrated a progressive decrease in size first apparent on the fifth day in the hospital. Normal dimensions were attained on the eleventh hospital day. Three weeks after admission the patient was discharged essentially well. The diagnoses were beriberi, beriberi heart with cardiac insufficiency, alcohol addiction, delirium tremens, and pellagra.

The patient was readmitted to the hospital on October 4, 1940, complaining of burning of his feet and slight tenderness of his calves of two weeks' duration. He stated that, since discharge, he had continued to take two to five pints of wine and some beer and ale daily. He had eaten very little food and for the past five weeks had discontinued the Brewer's yeast tablets prescribed on his discharge. His symptoms gradually became so severe that he was unable to walk so he returned to the hospital. Examination revealed marked tremors of his hands, hyperesthesia of his feet, and paresthesia of his soles. His blood pressure was 170 mm Hg systolic and 120 mm diastolic. There were no evidences of cardiac dysfunction on this admission. He was treated with thiamin chloride 10 mg four times daily, Brewer's yeast 5 gm daily. His symptoms disappeared and he left the hospital against advice on October 19, 1940. The diagnoses were alcohol addiction and polyneuritis.

Case 2 R J, a 23-year-old taxi driver, was admitted to the hospital on March 2, 1939, with the complaint of inability to use his legs, of five days' duration. For the past six years he had consumed about one-half pint of whiskey a day and during the past three months had increased this to one pint a day. This increase in consumption was apparently related to economic difficulties and personal maladjustment. He had noted a gradual disappearance of his appetite and for the past two months had subsisted on one cup of coffee and one to two sandwiches a day. During the three weeks just preceding admission he had had anorexia and he had vomited daily for two weeks. He began to notice progressive lameness in his legs and swelling of his feet. There was also some numbness and tingling in the fingers of his left hand in addition to generalized weakness. Five days before admission, he became much more irritable, "jumpy," and nervous. His condition became so alarming that he was taken to the Psychopathic Hospital where he had an attack of delirium tremens with typical tremors, overactivity, hallucinations and disorientation.

At that time he was found to have cardiac enlargement, edema, absent knee and ankle jerks, tenderness in the muscles of the arms and legs, great weakness of the arms and legs with coarse tremors and nearly complete paralysis from the waist down. With sedation and nursing care, he became mentally clear on the following day, but remained in the institution, where he was given a high vitamin diet, Brewer's yeast (8 gm t i d) and, on March 1, 1000 units of thiamin chloride subcutaneously and 300 units by mouth. He continued to be mentally clear, but his other disabilities persisted. After four days he was transferred to the Peter Bent Brigham Hospital on March 2, 1939, for further therapy.

Physical examination on admission revealed a very hyperactive, irritable, nervous young man complaining bitterly of pains in his legs. His temperature was 97.2° F, and respirations were 24. Pulse was 104, and blood pressure was 124 mm Hg systolic

and 62 mm diastolic. The skin was flushed, warm, and moist. The heart was moderately enlarged to percussion, and the heart sounds were loud with a suggestion of embryocardia. A high-pitched blowing systolic murmur and a systolic gallop rhythm were heard at the apex. A soft systolic murmur was heard over the aortic area. The pulse was fast and felt full and bounding. Moderate venous distention was visible in the neck. The lungs were clear. The liver was enlarged to percussion and somewhat tender. There was moderate pitting edema of the calves and marked pitting edema of both ankles. There was marked weakness and incoordination of all muscles of the legs without any obvious atrophy and no specific muscle paralysis. All the muscles of the thighs and calves were exquisitely tender to palpation, and there was marked tenderness along the peripheral nerves, especially the sciatic nerve. Motion in all joints was limited by extreme muscle sensitivity and weakness. There was numbness and partial objective anesthesia to light touch of the left forearm, the palm of the left hand, and the fingers.

Laboratory data on admission were: erythrocytes, 3,740,000, hemoglobin, 72 per cent, leukocytes, 7,300 (with normal differential distribution), Hinton and Wassermann reactions were negative. The urine showed no significant abnormalities. Phenolsulphonphthalein excretion was 66 per cent in two hours. The non-protein nitrogen of the blood was 57 mg per 100 c.c., the total protein 57 gm per 100 c.c., the albumin 2.9 and the globulin 2.8. A seven-foot film of the chest showed moderate cardiac enlargement, both to the right and left, with a rather straight left border. There was fairly marked pulmonary congestion around the hila and in the right base. The electrocardiogram showed normal curves.

The patient was placed on a high caloric, high vitamin diet with thiamin chloride, 12 mg subcutaneously daily and Harris yeast tablets, 4 gm t.i.d. Under this therapy, there was rapid and dramatic improvement in the patient's condition. He ran a moderate temperature elevation (101° F) for several days. By the third hospital day he was practically free from pain and was able to move his legs without hurting himself. Several days later no murmurs or gallop rhythm were audible over the heart, and by the tenth hospital day all edema had disappeared, and the patient was quite comfortable and able to sit up for short periods during the day. Erythrocytes and hemoglobin rose to normal values, and the non-protein nitrogen level returned to normal. Subsequent films of the chest revealed progressive decrease in the size of the heart and clearing of the lung fields. By the eleventh day of hospitalization, the heart was normal in size to roentgen-ray examination. Electrocardiograms continued to be normal except for some increase in the size of the T-waves. His improvement continued, and he was allowed increasing periods of walking, first with assistance and then alone. On his discharge March 30, 1939, 28 days after admission, the patient was able to walk fairly well, but exhibited considerable atrophy of the intrinsic muscles of the hands and forearms with moderate generalized atrophy of the muscles of the legs. He still had a moderate tachycardia. During the period of hospitalization his weight decreased from 71.6 kg to 58.6 kg. Most of this weight loss occurred during the first two weeks and could be explained for the most part by loss of edema fluid.

The patient was readmitted to the hospital on April 23, 1939, for observation. He had continued on Brewer's yeast daily and Harris yeast tablets 1 gm t.i.d. plus three teaspoonfuls of cod liver oil daily. He showed considerable improvement, was able to walk upstairs easily, and had noted a gradual disappearance of his limp. He had gained weight and felt well.

Physical examination revealed a fairly well nourished, calm individual. The skin was dry and cool. The heart and lungs were normal. The blood pressure was 115 mm Hg systolic and 60 mm diastolic, and the pulse rate varied between 100 and 110. The liver was somewhat increased in size to percussion, but was not tender. There was slight weakness of the legs. There was moderate tenderness to palpation in

TABLE I
Patient 1 (U L)

Date	Oxygen Consumption C c per Minute	Basal Metabolic Rate	Arterio-venous Oxygen Difference C c per Liter	Cardiac Output				Basal Heart Rate per Minute	Venous Pressure Mm HgO	Circulation Time Seconds	Vital Capacity C c	Weight Kg	Arterial Pressure Mm Hg	Blood Volume C c	Therapy
				Liters per Minute	C c per Beat	Liters per 100 C c Oxygen Consumed	Liters per Square Meter of Surface Area								
6/ 7/40									195	13 6 13 0	2500	67 1	128/84		10 mg thiamin chloride
6/ 8/40	268	+17			49 1	1 61	2 85	87						Plasma 3830 Red blood cell 2350 Total 6180 Hematocrit 37 9%	20 mg thiamin chloride
6/ 9/40	293	+28	{ 63 0 61 4	4 71				89	85						20 mg thiamin chloride
6/10/40					43 2	1 80	2 50	101		18 0	2900	60 3			10 mg thiamin chloride daily
6/11/40	280	+21	{ 70 8 64 0	4 15				90		15 0	3000				
6/12/40	246	+ 8		3 88	38 8	1 34	2 35	95				60 5	130/98		
6/13/40	289	+24	{ 73 5 75 4	3 95	41 1	1 40	2 39	94				59 5			
6/14/40	282	+23	{ 70 2 72 8					95	50	15 5	3000	58 5			
6/17/40	259	+13		3 56	37 1	1 39	2 16	93					124/90		
6/18/40	257	+13	{ 76 1 70 4 70 0						58	18 3		57 7		Plasma 2450 Red blood cell 2110 Total 4560 Hematocrit 46 3%	
6/21/40															
6/26/40	242	+ 6	{ 70 4 76 9 77 4	3 23	33 7	1 34	1 96	90			3050	57 3	122/92		Thiamin chloride discontinued
7/ 2/40	243	+ 5						82	65	26 5 24 7	3200	57 8	140/110		
7/ 5/40	227	- 2	{ 70 9 75 8	3 09	32 2	1 36	1 88	83				56 7	126/90		

the calf muscles Routine laboratory studies were not remarkable The patient was discharged on April 24, 1939, with instructions to continue his medication The diagnoses were acute alcoholic hallucinosis, beriberi (alcoholism), beriberi heart with cardiac insufficiency and neuritis due to beriberi

The measurements of the circulation in these two patients are set forth in tables 1 and 2, and graphically represented in figure 1

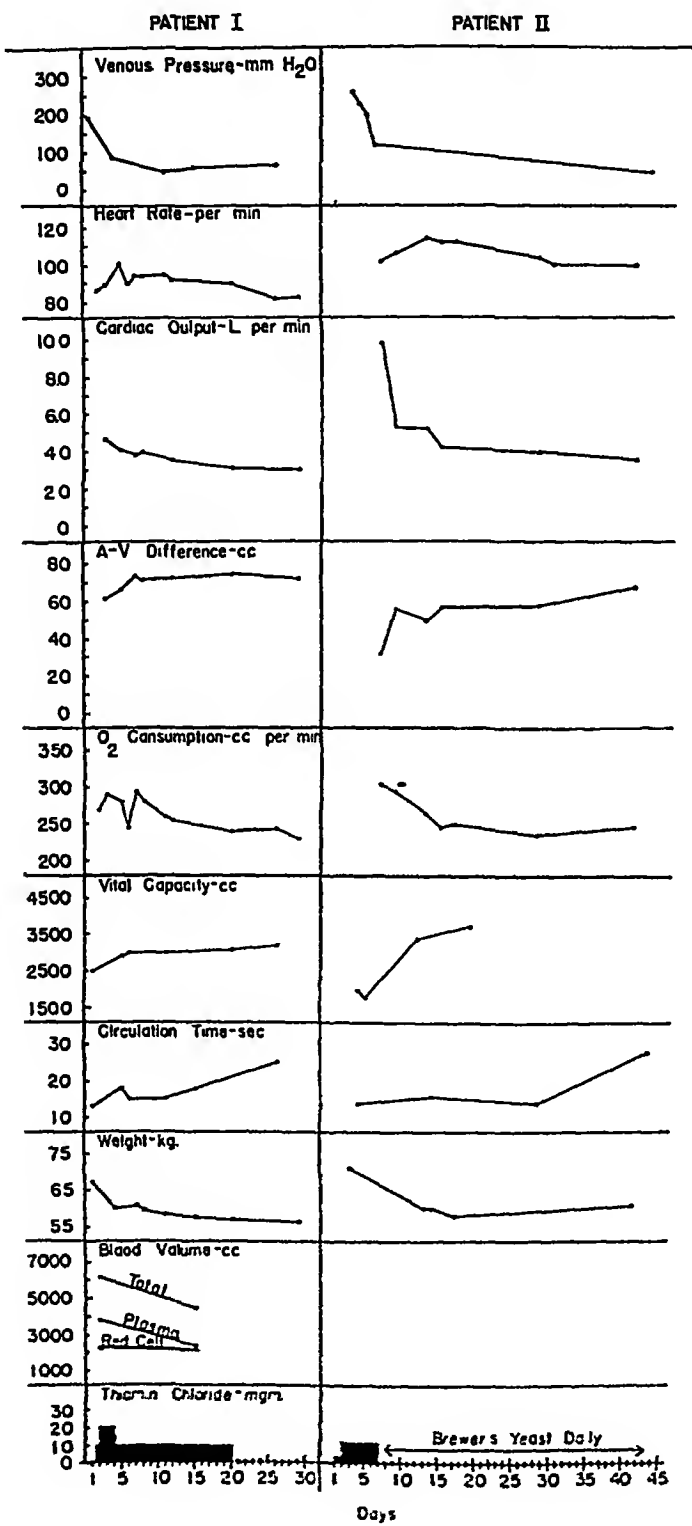


FIG. 1. Measurements of the circulation in patients 1 and 2 in relation to therapy

DISCUSSION

It is evident that both patients at the time of admission had frank congestive heart failure. This is concluded from the combination of elevated venous pressure, dependent pitting edema, reduction in the vital capacity, and roentgen-ray evidence of cardiac dilatation and pulmonary congestion. In neither case could the extensive edema be attributed to hypoproteinemia although in one the albumin was moderately reduced. The signs in each pointed to failure of both the right and the left ventricle, though predominantly the former.

Our observations bear out those of others that during congestive heart failure associated with vitamin B deficiency there may be an increased cardiac output, a low arteriovenous oxygen difference, an elevated venous pressure, and a shortened circulation time. During recovery there is a change toward normal of these measurable circulatory phenomena, viz., a decline in cardiac output, an increase in the arteriovenous oxygen difference, a fall in venous pressure and a prolongation of the circulation time. In addition, in one patient (Case 1), it was shown that during failure there was a marked increase in the plasma and total blood volume, both of which returned to normal during recovery. We also found in both patients an initially high oxygen consumption which likewise gradually returned to normal under observation. It may be argued that this high oxygen consumption accounted for the high cardiac output values, but the fact that the arteriovenous difference was abnormally low indicates that the cardiac output was increased out of proportion to the metabolic needs of the body. Roentgen-rays of the heart shadow in both cases showed the dimensions considerably increased beyond normal before therapy. Beginning a few days after the start of therapy there was a progressive decrease in the size of the heart shadows which gradually returned to normal limits within two weeks (figures 2 and 3). The electrocardiograms in both patients revealed essentially normal complexes at the beginning of observation and no definite change following therapy.

Although the initial value for the cardiac output was well above the average normal in patient 1 and in patient 2 was about twice the upper limit of normal, our data do not permit us to state with certainty that the cardiac output in either patient was above normal during the interval between admission and the time of our first observations. It would be of interest to have data on the cardiac output during this period because from the observations that we have at hand we are unable to say how much, if any, our initial measurements were modified by the short period of treatment preceding them. Other investigators have suggested from direct measurements of the cardiac output and indirect observations (accelerated circulation time, hot flushed skin and bounding pulse) that congestive failure occurring in vitamin B₁ deficiency is associated with a cardiac output that is above normal. It was likewise observed in our patients that the circulation time

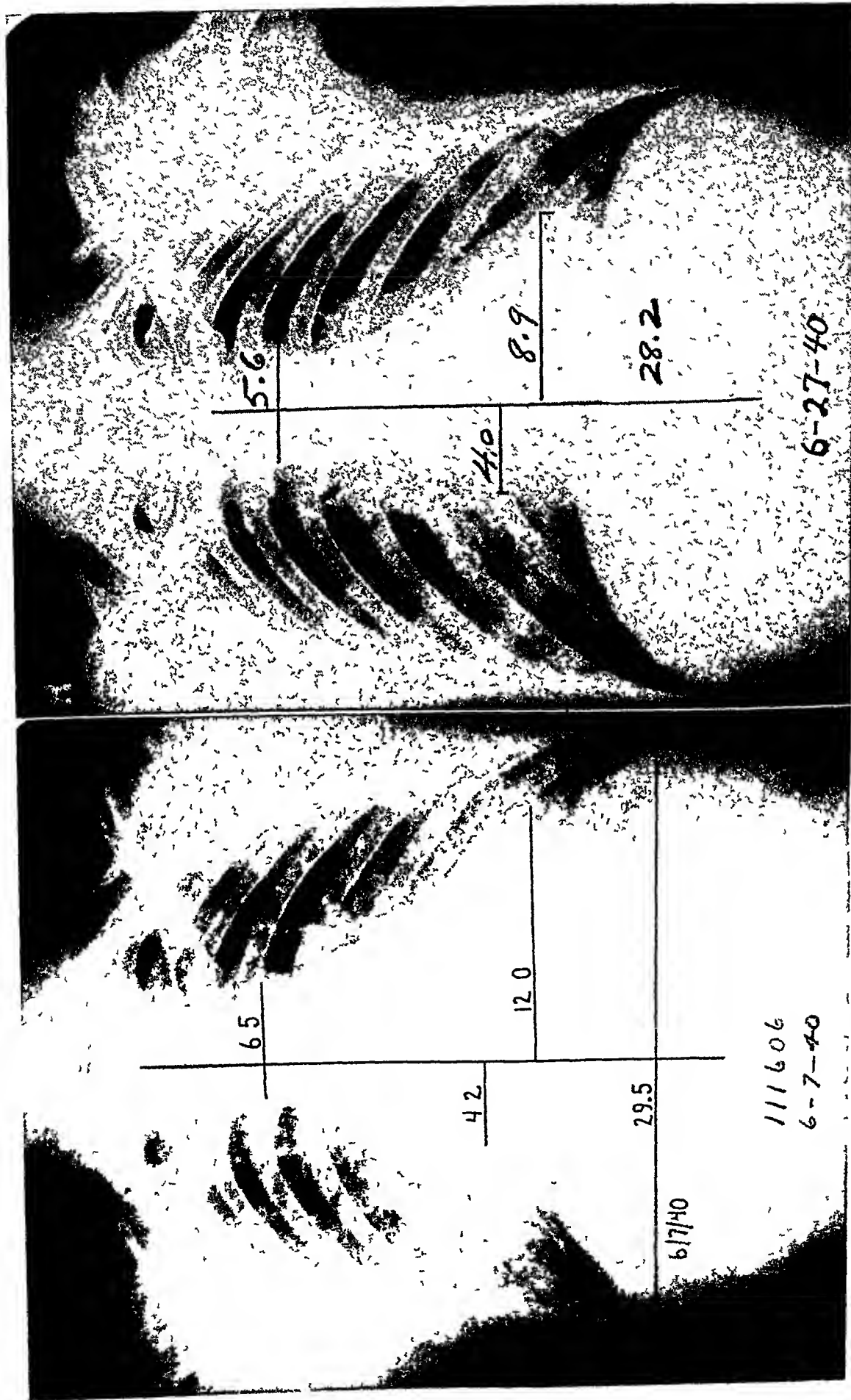


Fig 2 Roentgenograms of patient 1 on admission and 20 days after treatment was begun

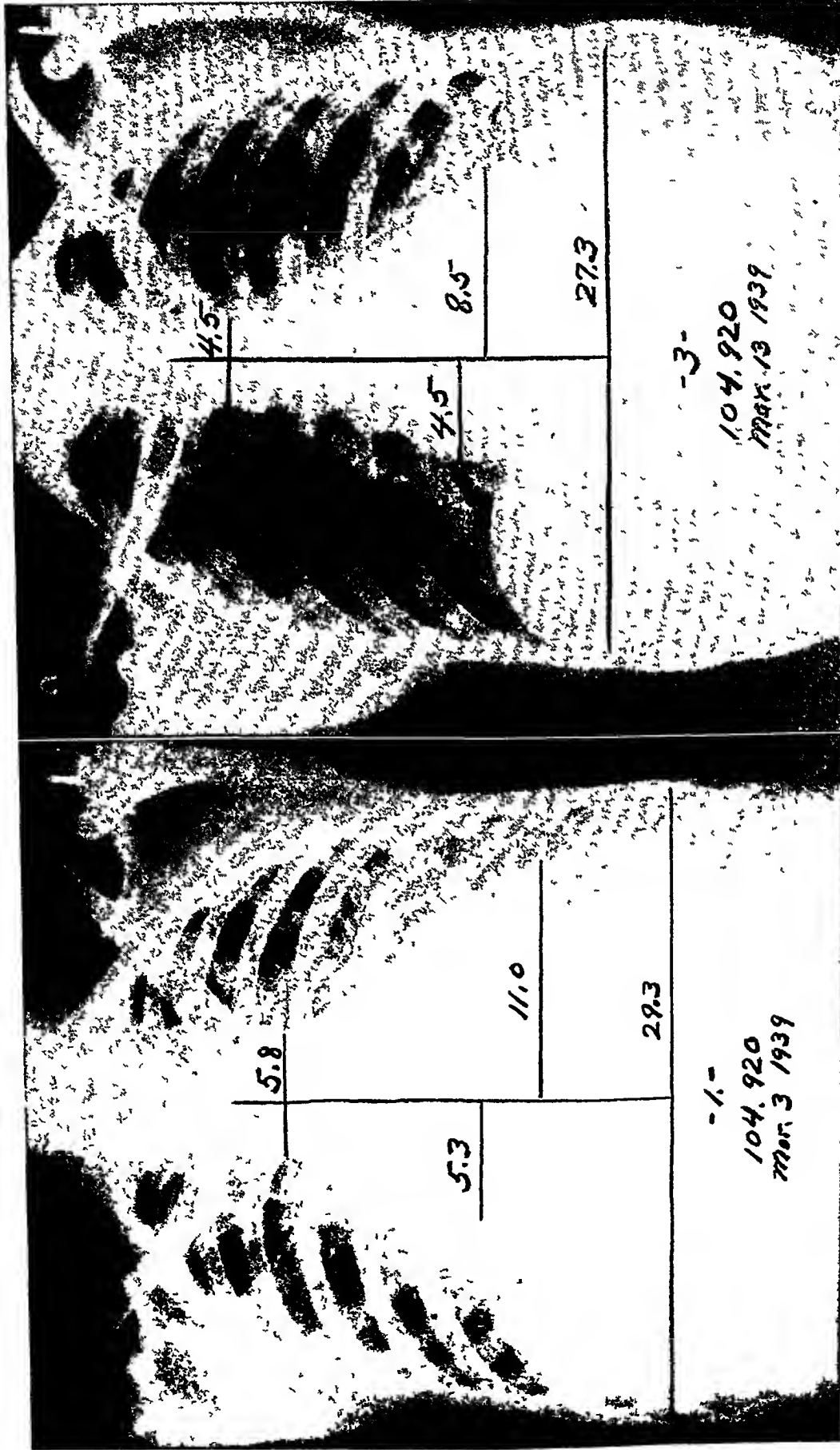


FIG 3 Roentgenograms of patient 2 on admission and 10 days after treatment was begun

was shorter during failure and that as recovery took place the circulation time became prolonged. It is probable, then, that the initial determinations of the cardiac output in our patients represent the approximate levels present before therapy was begun, but it must be admitted that these values may have been elevated to some extent by a further increase immediately following the start of therapy.

It is probable that recovery from heart failure due to B_1 deficiency is brought about by a combination of decreasing cardiac load and a more efficient myocardium. The elevation of systolic and diastolic blood pressure, the decrease in pulse pressure, and the slowing of the circulation which were observed after therapy was started are evidences that an increase in arteriolar tone took place during recovery. Weiss and Wilkins¹⁷ postulated that "arteriolar constriction following B_1 therapy must also react, in turn, centrally on the heart in the same beneficial manner as the closing of an arteriovenous aneurysm." Theoretically this change may bring about a decrease in the minute volume of blood returning to the right heart and hence would reduce one major factor in the amount of work required of the heart. Actually, such a decrease was observed. At the same time it is suggested by animal experiments and pathological material^{11, 14, 15} that thiamin deficiency may directly affect the myocardium, resulting in less efficient function and even failure at levels of work ordinarily handled with ease. Thus, it is probable that the administration of thiamin in our patients acted directly on the heart and that the action is to some extent responsible for the disappearance of the phenomena of congestive failure.

The finding of an initially elevated oxygen consumption which gradually returned to normal levels is subject to two interpretations. One is that the oxygen consumption is elevated in vitamin B_1 deficiency, and that our observations represent a gradual return to normal under therapy. The second is that, during deficiency, oxygen consumption is at a low normal level or below and that immediately following therapy there is a sudden and marked increase in this function and that our initial figures were determined at the peak of this rise. The only study of this function in human beings⁵ shows higher values during deficiency than after therapy and hence favors the former hypothesis. However, in one of our patients (Case 1), on two occasions there was a definite rise in oxygen consumption after the institution of therapy, reaching a peak on the third and sixth days of therapy. In the other patient, measurements of the oxygen consumption were not made until after the fourth day of treatment and this may account for the failure to observe the initial rise. In addition, experimental work on isolated tissues¹⁰ reveals a diminished oxygen uptake in deficiency and an increased metabolism on the addition of thiamin, and studies on the pigeon¹¹ and other animals show that oxygen consumption is decreased below normal during vitamin B_1 deficiency. These findings would tend to substantiate

the second hypothesis of compensatory increase in oxygen consumption following therapy. It is apparent that this problem needs further investigation before a definite conclusion can be reached.

SUMMARY AND CONCLUSIONS

Observations related to certain circulatory functions were made on two patients recovering from cardiac failure associated with vitamin B₁ deficiency. These observations showed increased cardiac output (with both a decreased arteriovenous oxygen difference and an increased oxygen consumption), elevated venous pressure, accelerated speed of circulation and, in the one patient in whom the determination was made, increased blood volume. These altered circulatory functions were observed to return to normal during the recovery period.

These observations are in accord with opinions expressed by others that the cardiac output is increased during congestive failure associated with vitamin B₁ deficiency. The observations suggest, furthermore, that one important factor leading to recovery from this type of cardiac failure is contraction of an abnormally dilated peripheral vascular bed.

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TULAREMIA

A REPORT OF THREE FATAL CASES WITH AUTOPSIES *

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THE purpose of this report is to submit clinical and pathologic studies of three fatal cases of ulcero-glandular tularemia, two of them being of the rapidly fatal primary septicemic variety and the third of longer duration

The first fatal case with autopsy was reported in 1924 by Verbrycke¹, and since then about 60 additional autopsy studies have been published² Duplications in the literature make it difficult to state the exact number of necropsy cases

CLINICAL PICTURE

The incubation period varies from a few hours to 13 days, but it is usually from two to five days In the cases reported below the primary sore or constitutional symptoms appeared within five days In 90 per cent of the cases a primary lesion develops at the site of inoculation as a small papule which rapidly enlarges and ulcerates leaving a punched-out ulcer with a necrotic floor There is usually a primary bacteremia which persists for seven to 10 days and results in the formation of focal necroses in the lung, liver, spleen and lymph nodes Regional lymph node involvement results from the direct extension of the organisms along the deep lymph channels, resulting in enlargement of these nodes in 90 per cent of the cases Occasionally, as in two of our series, this primary bacteremia is a septicemia from the onset in an individual who has little or no natural resistance, resulting in death within 14 days

This primary bacteremia usually disappears as antibodies are developed Likewise, the areas of necrosis in the lungs, liver, etc, heal with scar formation as resistance appears As most deaths occur at a later stage and on the basis of considerable cultural and necropsy evidence, Foshay, Francis, and other leading students of the disease have postulated that there is a second blood stream invasion in the majority of the fatal cases This septicemia arises from any one of the previously established areas of necrosis by ulceration into a blood vessel or by direct invasion from the lymph tissue to the blood stream This septicemia results in the production of countless areas of necrosis which may appear in any organ, but chiefly in the liver, spleen, lungs, and lymph nodes

The onset is frequently abrupt with chills, fever, sweats, headache, malaise, and various gastrointestinal symptoms Great prostration is the rule The primary lesion with regional adenopathy is present at the onset or ap-

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pears in 24 to 48 hours This lesion is most often found on the fingers or hand but may appear on any part of the body coming in contact with the invading *Bacterium tularensis* Visible lymphangitic streaks appear only when there has been secondary infection of the primary lesion Fever is always present and averages 102° to 104° F ; its duration in uncomplicated cases is from two to four weeks When complicated by pneumonia or suppurating buboes it may last several months Cough is an early and tran-

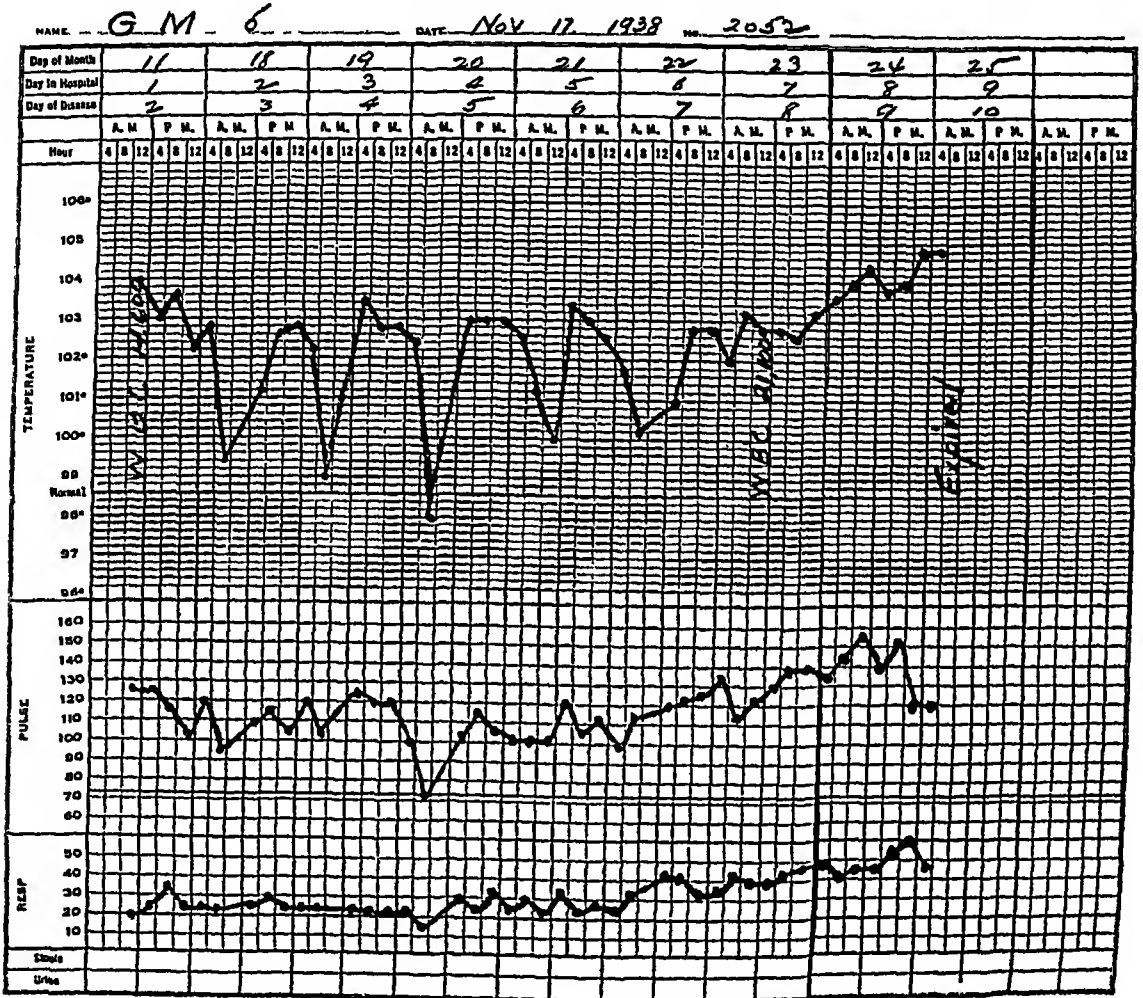


FIG 1 Clinical chart of Case 1 Note the leukocytosis and evidence of severe infection Duration of illness 10 days

sient symptom and disappears by the second week Clinical signs of pulmonary lesions occur in at least 18 per cent of the cases and about an equal number develop pleural effusions Pulmonary signs may be present at the onset of the disease, but more frequently they appear after the initial symptoms The physical signs are variable; they appear and disappear from day to day unless the process has become massive Usually both lungs are affected but the signs are, as a rule, more marked on one side than on the other At first the signs may be those of capillary bronchitis with the presence of fine crepitant râles and the absence of definite areas of dullness As

the lesions progress, patches of impaired resonance with coarser râles will be found. As the process coalesces, actual dullness with tubular breath sounds is noted. These changes, as portrayed, are extremely variable. The course may be fulminating and terminate fatally in a few days or progress slowly over a period of weeks. If recovery occurs, the signs clear very slowly, persisting for a long time after constitutional symptoms have disappeared.

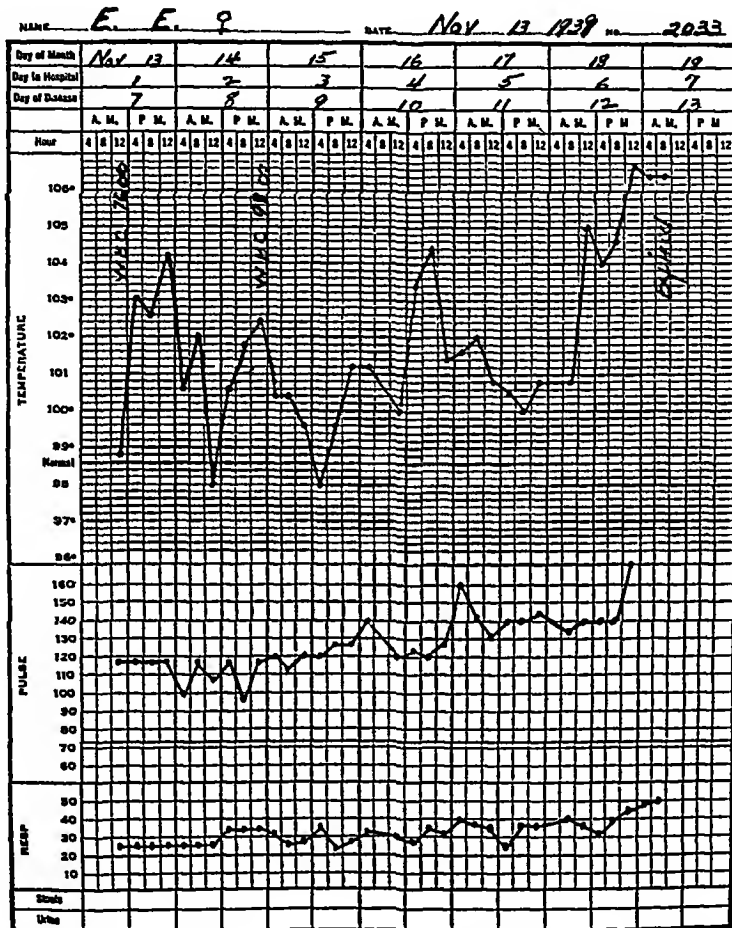


FIG 2 Clinical chart of Case 2. Note the absence of leukocytosis.

Pleural effusion may occur at the onset, but more frequently appears during the course of the infection. The effusion may or may not be associated with intrapulmonary involvement. The fluid is exudative in character with lymphocytes predominating in the cell count. The *Bacterium tularensis* has rarely been demonstrated in the fluid, but it may cause agglutination of the organism in high dilutions. With pleural fluid occurring alone at the onset of the disease the difficulties in differentiating this disease from tuberculosis are obvious.

Besides capillary bronchitis, bronchopneumonia, and lobar pneumonia, the process may present the signs of lung abscess. For a period of a week or more there may be a single area of moderately impaired resonance with



FIG 3 Roentgenogram of chest of Case 3, showing pulmone consolidation in upper right lobe

harsh or definitely tubular breath sounds, and roentgenograms may present the typical picture of a solitary abscess. This lesion may progress to cavity formation or slowly regress. If the disease progresses slowly throughout both lungs the signs may be those of multiple cavitation.

Recovery occurs in approximately 94 per cent of the cases but the convalescence is often prolonged over a period of months even in the absence of complications

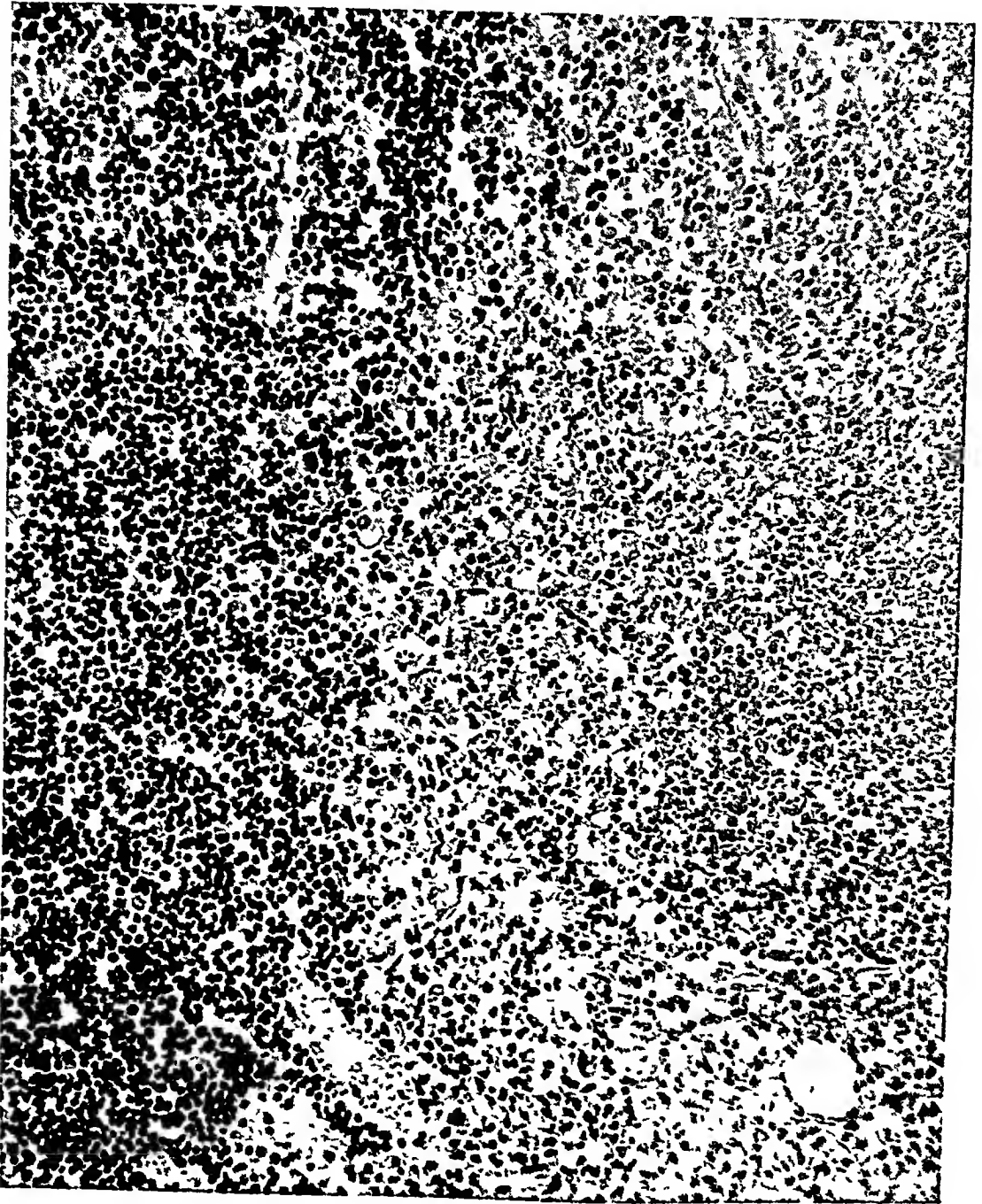


FIG 4 Axillary lymph node demonstrating the margin of an area of coagulative necrosis. This is an early stage in which the nuclei in the necrotic area covering the right three-fifths of the illustration exhibit pyknosis and karyorrhexis, whereas viable hyperplastic lymph nodal tissue constitutes the left two-fifths. Note absence of encapsulation. Ten days after onset.

The clinical features seen in patients with a primary septicemia are somewhat different from those of the average case in which the individual develops a degree of immunity. Man possesses very little natural immunity but is usually capable of developing protection in time to prevent his destruc-

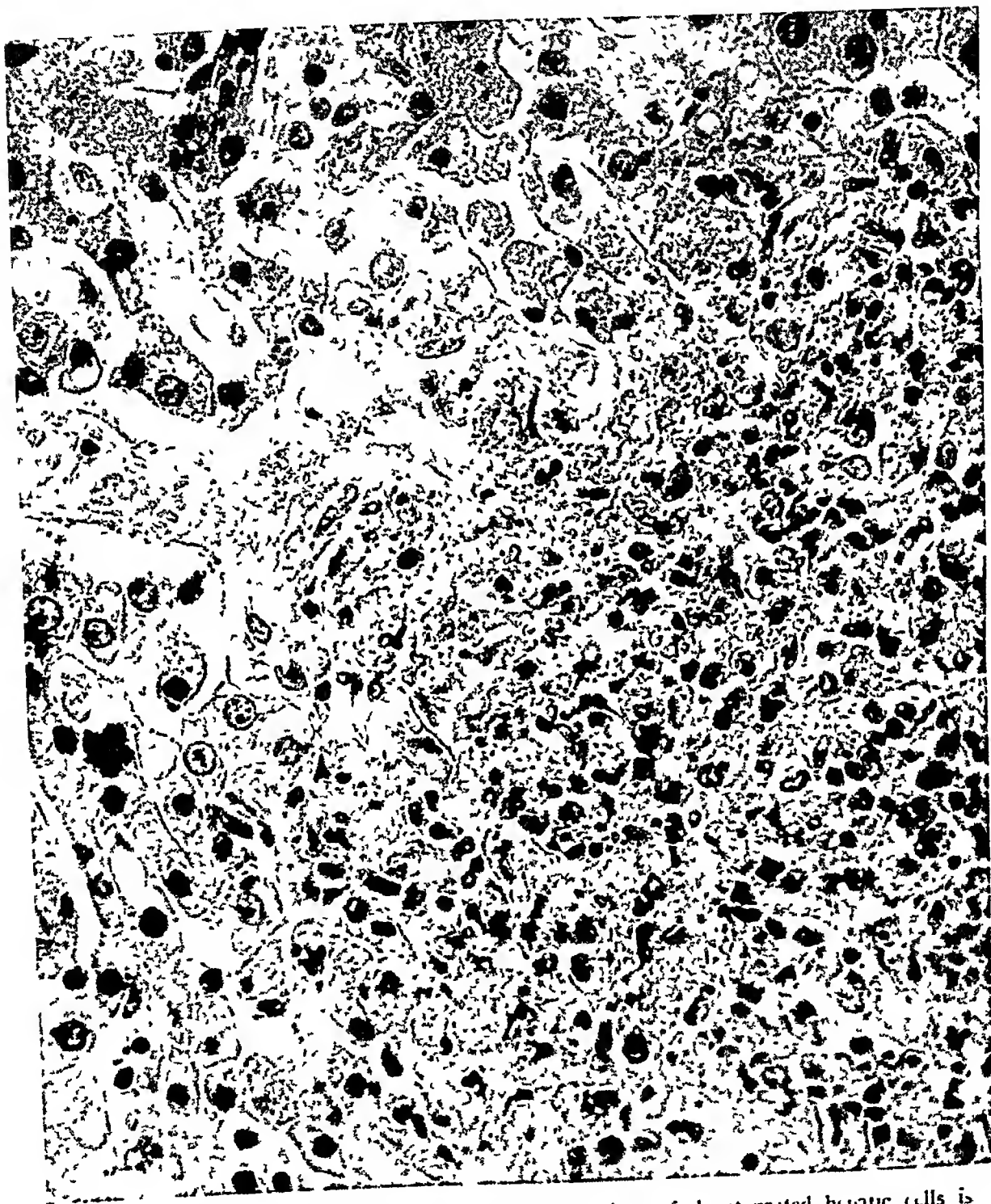


FIG 5 Liver. A focal necrosis in which the debris of disintegrated hepatic cells is mixed with lymphoid cells and histiocytes which have wandered into the area, most of which are pyknotic or fragmented.

tion There is, however, a small percentage of individuals who cannot develop this protection and therefore succumb to tularemia within a fortnight or less, as is characteristic of the disease in rodents In this group the primary bacteremia is maintained as a septicemia until the victim dies A patient with a primary septicemia has the usual incubation period but with the onset of clinical symptoms becomes desperately ill with great rapidity There are repeated drenching and debilitating sweats following the sharp chills The fever curve presents either marked fluctuations or maintains a high level The patient is prostrated, and there is severe malaise Usually there is marked tympanites, slight jaundice, slight splenomegaly and hepatomegaly Cyanosis and a slight cough herald the approach of pulmonary involvement which frequently progresses to bronchopneumonia Delirium occurs early, and the patient rapidly progresses to coma and death Other findings that occasionally occur are diarrhea, renal changes of hemorrhagic nephritis, and inflammation of the peritoneum, pleura, and pericardium

The diagnosis of tularemia is established by culture of the primary lesion, blood culture, agglutination studies and by skin tests, however, at times it is exceedingly difficult to demonstrate the presence of the causative organism, particularly in the rapidly fatal cases Culture of the primary lesion is unsatisfactory at times because of partial healing or secondary invasion of contaminating organisms which obscure the *Bacterium tularense* This organism grows slowly, frequently requiring four days for recognition This factor adds to the difficulty of making the diagnosis by means of blood cultures because in the severe septicemias the patient may die before growth appears Agglutination tests do not become positive before the second week and frequently much later The chief advantage of the agglutination test is that it becomes positive in 100 per cent of cases and persists for many years after recovery A titer of at least 1:80 is necessary for diagnosis unless there has been a previous negative agglutination Cross agglutination with *Brucella abortus* and *Bacillus proteus* OX-19 may cause some difficulty in rare instances Huddleson's phagocytic test is of value in those instances in which this cross agglutination with the *Brucella* group occurs Foshay³ has described antigen and antiserum skin tests The former is ideal from a diagnostic standpoint and is now commercially available The antiserum test is claimed to have the same high accuracy as the antigen test (100 per cent positive before agglutinins appear) but this point is disputed by Friedewald and Hunt⁴

PATHOLOGIC STUDIES

The internal organs most frequently and severely affected by the invasion are the lymph nodes, lungs, liver and spleen

The structure of the involved lymph nodes varies with the stage of the disease Hyperemia, edema, reticuloendothelial hyperplasia and aggrega-

tions of lymphocytes, plasma cells and macrophages in the sinuses lead to a loss of distinction between sinuses and medullary cords in the earlier stages. Here, too, areas of coagulative necrosis and karyorrhexis, beginning in the cellular aggregates within the sinuses, extend to constitute grossly apparent

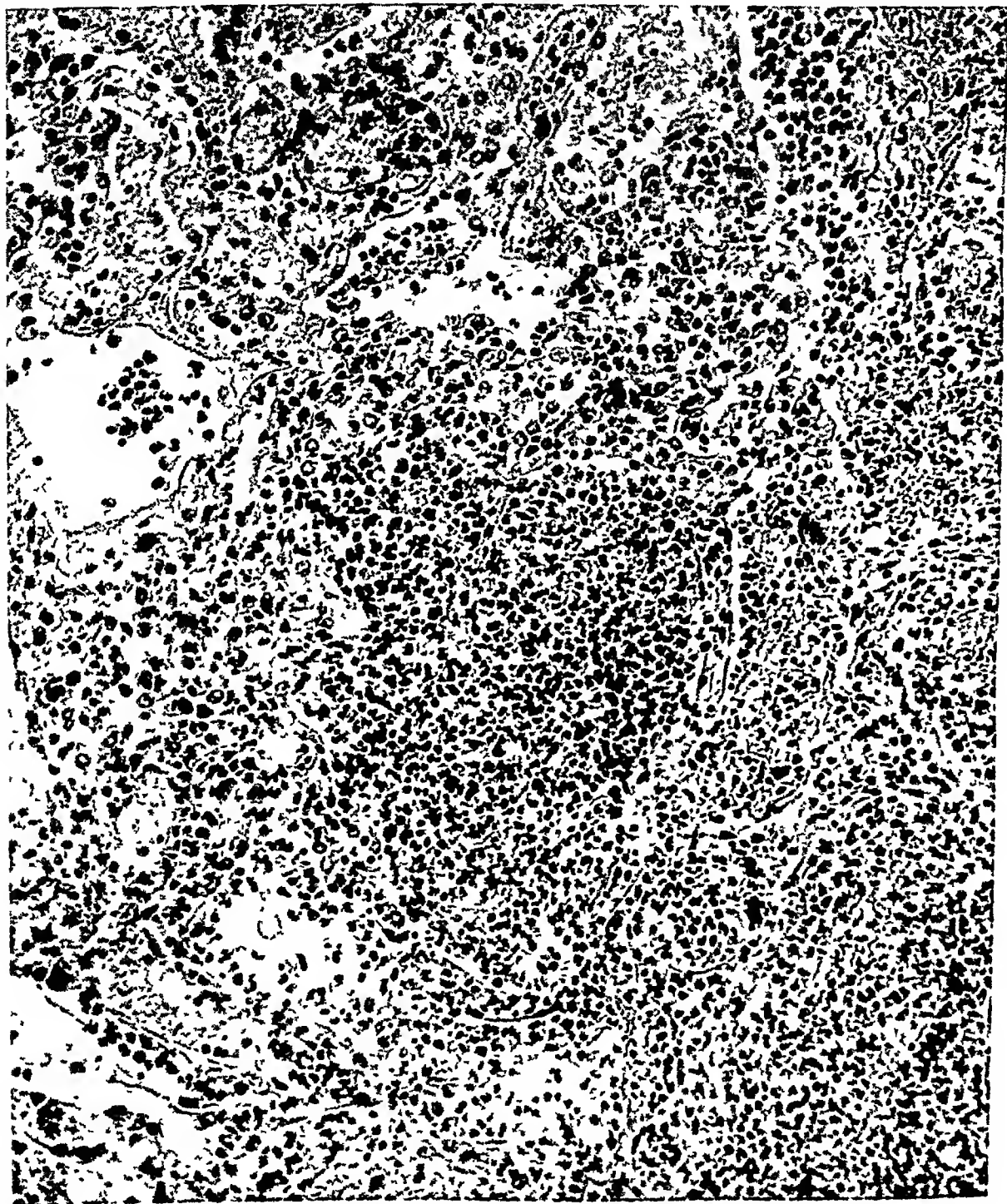


FIG. 6. Lung. This shows beginning coagulative necrosis. An intra-alveolar exudate of lymphoid cells and macrophage histiocytes is undergoing pyknosis and karyorrhexis. Later it will be represented by dense amorphous debris which, with the further disintegration of alveolar walls (here begun), will comprise bulky areas of necrosis, grossly caseous.

areas of caseation Vascular thrombosis, areas of hemorrhage, fibrin and polymorphonuclear leukocytic exudation (this infrequently) may be found Progression of the disease is accompanied by encapsulation of the areas of necrosis by epithelioid cells, often in palisade-like arrangement, with lymphocytes and various histiocytes peripherally, and in this cellular periphery one or more multinucleated cells may be found, often with a mural distribution of nuclei Replacement of the epithelioid cells by fibroblasts, which proceed to form a fibrous wall about the areas of caseous necrosis, marks the later stages

Pulmonic lesions are present in over 90 per cent of the fatal cases, with involvement of one or more lobes Although occasionally of lobal distribution, they are usually focal or confluent Two general types of lesions are described pneumonic and localized caseous necrosis However, areas of necrosis can be found within pneumonic areas, and it is possible that all tularemic pulmonic lesions have a common pathogenesis, that all areas of localized necrosis develop as a progressive coagulative necrosis of intra-alveolar exudate and alveolar septa This exudate is chiefly of monocytes, lymphocytes, histiocytes and plasma cells, polymorphonuclear leukocytes predominating only in instances of secondary infection with pyogenic organisms Liquefaction of the necrotic debris may occur, leading to cavity formation Hyperemia, edema, interstitial inflammatory infiltration, bronchiolitis, proliferative and thromboangitic vascular lesions are variable features Interstitial, serous, fibrinous and proliferative pleuritis, alone or in combination, may occur

The liver is generally somewhat enlarged, the average in our three cases being 1,950 grams There is nothing remarkable in the gross appearance except the presence of multiple focal lesions that average 1 to 3 cm in diameter These spots are gray or yellowish in color and are less numerous in the liver than in the spleen These lesions consist of coagulation necrosis of parenchyma with invasion of histiocytes, lymphocytes and occasional polynuclear leukocytes In the remaining parenchyma there is evidence of toxic degenerative alteration

The spleen is usually congested in cases dying during the first month, afterwards the enlargement is not found as frequently Many foci not unlike those found in the liver are common in the early fatal cases These foci tend to disappear after the first month in patients that live longer Clumps of cells are numerous in the pulp, consisting of lymphocytes, plasma cells and polynuclear leukocytes The caseous foci resemble those found in the liver Reticuloendothelial hyperplasia is found in at least one third of the cases The follicles are generally small and hypoplastic

CASE REPORTS

Case 1 G M, a white male aged 43, was admitted to the York Hospital on November 17, 1938, with a temperature of 104° F Five days previous to admission he had shot and cleaned two apparently healthy rabbits, three days later he had severe

chills and fever, nausea, intense headache, drenching sweats and marked diarrhea. He also noted pain in the region of the left thumb. On admission the man appeared desperately ill with high fever and rapid pulse, but the respirations were normal. The liver and spleen were not enlarged. The left thumb tip was tender with a brawny appearance. There was no lymphangitis but there was a nest of tender enlarged nodes in the left axilla, no other enlarged nodes were found. Blood studies were normal except a white cell count of 14,000 of which 58 per cent were segmented and 20 per cent were non-segmented neutrophils, the remaining cells were lymphocytes. Repeated blood cultures remained negative and agglutination studies were normal. The patient appeared extremely intoxicated, he had repeated chills and sweats and a septic type of fever. He became irrational three days after admission. The lymph nodes in the axilla continued to enlarge and two days before death he developed a slight cough with signs of bronchopneumonia which was confirmed by roentgen study. The duration of his illness was 10 days. A few days after death the last blood culture revealed *Bacterium tularensis*.

Postmortem examination was performed by Dr. Lewis C. Pusch, Pathologist to the York Hospital. The left axillary nodes were enlarged and contained caseous areas. The bulky areas of caseous necrotic cellular debris were bordered by histiocytes and lymphocytes. Each lung weighed 930 grams and was moist and dark red on gross section with a scattered distribution of grayish-brown areas of consolidation three to four cm in diameter. Microscopically there were broad caseous masses of necrotic cellular debris bordered by alveoli filled with histiocytes and fewer leukocytes. The spleen showed many small mottled caseous foci identical in structure with those of the nodes and lung. The liver weighed 1910 gm and showed an occasional focus similar in appearance to those described above. Smears of the exudate of the thumb, nodes and spleen revealed very small gram-negative organisms of bacillary and coccoid forms.

Case 2 E. E., a white housewife aged 52, was admitted to the York Hospital on November 13, 1939. On November 1, without using gloves she had cleaned several wild rabbits which her husband had shot and eviscerated. When handling the carcasses the husband had worn rubber gloves, but the patient had failed to observe this precaution. Five days later she noted malaise, slight fever, anorexia and severe headache. There was a bleb-like lesion on the right thumb which appeared with the onset of the disease and persisted throughout the course of the illness. The symptoms noted above gradually became more marked, and her temperature became septic in type. Physical examination revealed severe intoxication with a temperature of 103° F, pulse 118, and respirations 26 per minute. On the right thumb there was an ulcer 1.5 cm in diameter with no lymphangitis, but in the right axilla there was a small nest of tender lymph nodes. Other than some distention of the abdomen and slight enlargement of the liver the findings were not remarkable. Initial laboratory studies revealed a small amount of albumin in the urine, mild hypochromic anemia with a leukocyte count of 7,600 with a normal differential count. Blood Kahn reaction was negative, as were all agglutination studies. Culture of the ulcer showed *Staphylococcus aureus*, and repeated blood cultures were sterile. The patient's course was rapidly downward and she lapsed into a stuporous condition. Repeated laboratory studies were essentially the same as on admission. She was treated with full doses of sulfonamides and repeated blood transfusions. She died 13 days after the onset of symptoms.

Postmortem examination by Dr. Pusch showed an enlarged right axillary lymph node, 2 cm in diameter, which contained caseous foci. The node was markedly edematous and hyperemic with but little distinction between sinuses and medullary cords. The former were filled with lymphocytes, plasma cells, and macrophagic wandering cells, some of which contained phagocytized nuclear debris. The caseous

foci noted grossly consisted of areas of coagulative necrosis with karyorrhexis and little peripheral reaction. No areas of suppuration and very few polynuclear leukocytes were seen. The pericardial cavity contained about 50 cc of serosanguineous fluid, the heart and vessel were normal. About 450 cc of serosanguineous fluid were found in each pleural cavity. The pleural surface was covered with fibrin. The right lung weighed 590 gm, and the left one 510 gm. The bronchial tubes had grayish-red mucosae with gray coagulated exudate in the lumina. The tracheo-bronchial nodes were anthracotic. Cut surfaces of the lower lobes were moist, dark red and partly atelectatic. The upper lobes were moist and grayish-red. Several sharply circumscribed caseous white foci of irregular contour were found. Their diameters varied from 2 mm to 2 cm. Although scattered throughout both lungs, they were seen chiefly in the lower lobes. The pulmonary capillaries were engorged with blood. Many alveoli were filled with plasma. The caseous white areas resembled those of the lymph node. Little or no phagocytized blood pigment was seen. The smallest and earliest lesions consisted of foci of lymphocytes and wandering cells with beginning karyorrhexis. The tracheobronchial lymph nodes were characteristic of tularemic lymphadenitis. About 200 cc of serosanguineous fluid were obtained from the peritoneal cavity. The gastrointestinal and biliary tracts, pancreas, and adrenal glands were not remarkable grossly, but the latter showed a marked toxic degenerative alteration, characterized by cytoplasmic swelling and vacuolation zona fasciculata of the cortex. The liver weighed 1,950 gm, it was relatively homogeneous except for a scattered distribution of small white foci, 1 to 3 mm in diameter. These foci resembled those in the lungs and nodes on histologic examination. The hepatic cells showed marked cytoplasmic swelling. The spleen weighed 690 gm and presented scattered small solid white foci, 1 to 5 mm in diameter, otherwise it was unremarkable. These focal necroses were not unlike those described above. The kidneys showed a toxic reaction with cytoplasmic swelling of the tubular epithelium. Bacteriology. Minute coccoid Gram-negative bacilli, in clumps, were present in smears of lesions in the axillary node and in the lungs, morphologically characteristic of *Bacterium tularensis*.

Case 3 C D, white male aged 35, was admitted to the York Hospital on November 19, 1938. During the first week in November he hunted rabbits and was successful on three different days. One week after the last hunting episode he developed a blister on a finger that healed spontaneously in a short time. About the same time he also developed what was thought to be an acute respiratory infection with chills, fever, sweats and general malaise. These generalized symptoms gradually increased in intensity, with severe headaches, and he was forced to stop work and go to bed. At no time was there any evidence of lymphangitis or lymphadenopathy. During the first week of the illness he noted a pain in the right chest, accentuated by deep breathing, reddish sputum and cough. The past medical and family history had no particular significance, the patient was a machinist by occupation. On admission he had a fever of 103° F, with normal pulse and respiratory rate. The only abnormal features were slight impairment of resonance and prolongation of the breath sounds in the upper half of the upper right lobe and slight enlargement of the liver. These lung changes were confirmed by roentgen studies of the chest which revealed an area of consolidation in that region. Blood count was normal except for 17,200 white blood cells, with a normal differential count. All agglutinations were normal except for *Bacterium tularensis* which was positive 1:320. Blood Kahn reaction was negative. Sputum studies showed a large number of spirochetes and fusiform bacilli with many micrococci of the *Micrococcus catarrhalis* group, no acid-fast bacilli and very few pneumococci were found. Blood culture positive for *Bacterium tularensis*. During the first week the patient ran a septic course with enlargement of the pulmonary consolidation on roentgen-ray examination and a drop in the leukocyte count to 7,500.

His clinical course was progressively downward in spite of repeated blood transfusions, sulfonamide medication in full therapeutic doses and other supportive treatment, during this period he showed extreme toxemia with a septic temperature, marked malaise and drenching sweats. During the fourth week in the hospital he developed marked edema of the right leg with large purpuric spots and right inguinal adenopathy. This was associated with distention of the abdomen and enlargement of the superficial abdominal veins. On the arms and abdomen ecchymotic spots appeared rapidly and became larger, at places they were confluent. No part of the body was free from this condition except the scalp. On a little finger a nodule appeared which rapidly ulcerated and from which a purulent discharge was cultured and revealed, along with a dense and varied bacterial flora, a Gram-negative bacillus compatible with *Bacterium tularensis*. Ulceration developed over various parts of the body which yielded identical bacterial findings. During the course of the illness repeated blood cultures were positive for *Bacterium tularensis*, and the agglutination test arose to a high titer. The roentgen and clinical studies of the lungs showed a progressive spread of the consolidation with cavitation to other parts of the chest. The patient died of toxemia on the seventieth day of the illness. In spite of three transfusions a week in which 60 donors were tested or used the blood count dropped progressively to a severe anemia, with hemoglobin 5 gm, red blood cells 1.2 million, and white blood cells 14,700, with 42 per cent segmented, 33 per cent non-segmented neutrophils, 22 per cent small lymphocytes and 3 per cent monocytes.

Postmortem examination by Dr. Pusch. There were cutaneous ulcers of the right side of the face, back, ear, over the iliac crests, the little finger of the left hand, right leg and toes. The ulcers were in most part dry, and in part moist, foul, and sloughing. Some extended only into the subcutaneous fascia and others into muscle. The right pleural cavity was nearly obliterated by fibrous adhesions. The right lung weighed 1300 gm. All three lobes were ramified by irregularly shaped communicating zones of firm brownish-gray caseation from less than 1 to 3 cm in diameter. Intervening pulmonary substance was firm and grayish-red but partly aerated. Irregularly shaped cavities from a few millimeters to 6 centimeters in diameter were scattered throughout the lung, the largest occurring in the lower lobe. Some contained a thick white exudate, others a rather thin reddish-gray exudate. The linings were in part soft and reddish-black, others were granular and gray with no appreciable wall except that of adjacent pulmonary substance, which in some places was caseated and in others grayish-red and partly aerated. Mediastinal nodes were anthracotic. The left lung weighed 840 gm. It was heavy, moist, predominantly red, not firm, with a cavity 8 cm in diameter in the lower lobe, irregular in shape with a soft grayish-black lining and a wall of adjacent pulmonary substance. Microscopically the areas of consolidation consisted in part of broad areas of coagulation necrosis, in part of alveoli filled with polynuclear leukocytes, and in part of alveoli occupied by a network of fibrin enmeshing scattered leukocytes and histiocytes. Areas of consolidation were not homogeneous but included scattered aerated alveoli. The cavities were lined in part by tissue which had undergone coagulative necrosis, elsewhere by masses of polynuclear leukocytes. The linings generally were continuous, with similar structures in adjacent areas of consolidation, but in some areas a zone of epithelioid histiocytes intervened. Perivascular and intramural infiltrations of leukocytes and histiocytes in the walls of blood vessels were prominent features. Apparent lipid distention of the cytoplasm of many phagocytes was noticeable. Capillary engorgement was fairly generalized. In some areas, chiefly in atelectatic zones about cavities, proliferation of histiocytes lining the alveoli was conspicuous. The heart, large blood vessels and the anthracotic lymph node were unremarkable. The gastrointestinal and biliary tracts, kidneys, pancreas, and adrenal glands were unremarkable. Enlarged mesenteric nodes were found but were not abnormal on section. The liver weighed 1,750 gm, with

no visible necrotic foci, on section there were focal aggregations of histiocytes, lymphocytes and a few polynuclear leukocytes of variable localization resembling the focal hepatic lesions of typhoid fever, there was a moderate degree of toxic degenerative alteration. The spleen weighed 340 gm, with no visible focal lesions. On section there was reticuloendothelial hyperplasia. Sections of the adrenals showed cytoplasmic swelling of the cortical epithelium. Bacteriology. Smear of the white purulent exudate in the cavity in the upper lobe of the right lung showed staphylococci and an occasional intracellular group of minute Gram-negative coccoid bacilli.

SUMMARY

- 1 The clinical details of tularemia have been considered, with a description of the rather common pulmonary complications.
- 2 The clinical features of the primary septicemia cases are compared with the average case of tularemia.
- 3 The laboratory diagnosis of the disease is described.
- 4 Pathologic studies of the lymph nodes, lungs, liver and spleen are considered.
- 5 Three case reports of autopsied cases are reviewed.

I am indebted to Dr Lewis C Pusch, Pathologist, York Hospital, for many helpful suggestions in preparing the pathologic studies of this report.

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THE DETECTION OF SUBCLINICAL SCURVY OR VITAMIN C DEFICIENCY¹

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CLINICALLY classical scurvy is uncommon although cases are still encountered occasionally in infants and less frequently in adults. Is there a lesser degree of vitamin C deficiency which undermines health but is not manifest as scurvy? Nutrition is one factor over which we have some control. Optimal health is, of course, the goal of medicine and it assumes particular importance in times of national stress. If the vitamin C nutrition is suboptimal in any considerable portion of our population it is important that we should know it and define methods for its recognition.

Considered from a biochemical standpoint there is a wide variation in the nutritional status of various individuals relative to vitamin C. In any large series of cases, the concentration of ascorbic acid in the blood will be found to range from 0 to 1.3 mg per cent. This latter value reflects a state of saturation. If vitamin C is administered to an individual so saturated the blood plasma concentration rises above this level and ascorbic acid is excreted in the urine. Although there is some variation, a plasma concentration of 1.3 mg per cent represents the usual renal threshold.

Evidence is clear that the fasting plasma ascorbic acid level reflects the intake of vitamin C^{1,2}. Naturally if the plasma ascorbic acid value is found to be near the saturation level, vitamin C deficiency does not exist. If, on the other hand, the plasma ascorbic acid is low it does not necessarily indicate that the individual has suffered from the effects of vitamin C deficiency.

In this study we have undertaken to determine the degree of tissue depletion existing in cases with low plasma ascorbic acid values and whether or not this depletion has deleteriously affected the health of these individuals. Observations in this report deal only with adults.

Determination of the Vitamin C Deficit The determination of the tissue reserves of vitamin C is relatively simple. If an individual with reasonable saturation of tissue is given a large test dose of ascorbic acid, the concentration of this substance in the blood plasma will rise, reaching a peak usually in two and a half or three hours, and a portion of the ascorbic acid will be excreted in the urine. If, on the other hand, the tissues are severely depleted there will be only a slight rise in the blood plasma ascorbic acid concentration and none will be excreted. Intermediate degrees of saturation

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give intermediate curves (figure 1) In this study we have used a standard test oral dose of 15 mg of ascorbic acid per kilogram of body weight After determination of the fasting plasma ascorbic acid level the test dose is given and the plasma concentration is again determined at three and five hours The amount of ascorbic acid excreted in the urine during the five hour period is also determined For the sake of simplicity the resulting blood plasma curves can be classified as flat (peak below 0.5 mg per cent), medium (peak 0.5 to 0.9 mg per cent), or high (peak above 0.9 mg per cent) as shown in figure 1 Following this test the individual is given a known daily supple-

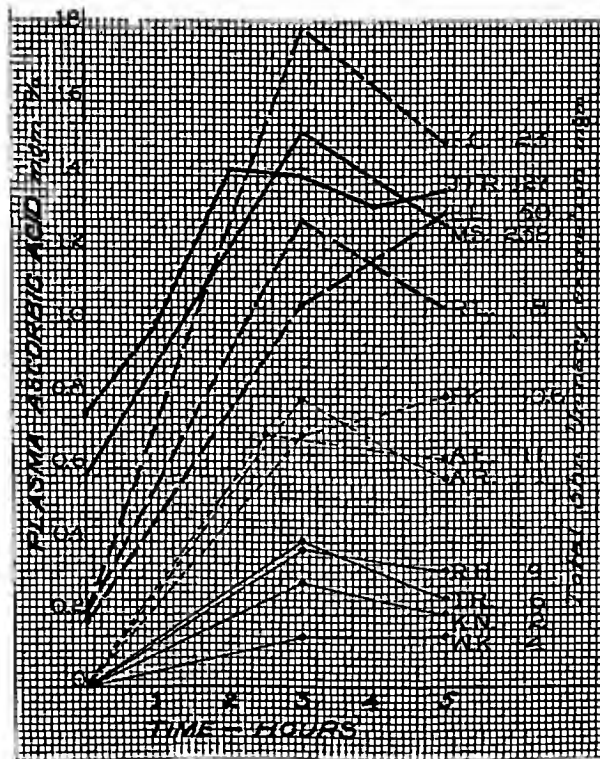


FIG 1 Curves of plasma ascorbic acid concentration following test doses of 15 mg per kilogram

ment of ascorbic acid, and check determinations of the fasting plasma ascorbic acid concentration are made at intervals When the fasting plasma level is at or near 1 mg per cent saturation has been achieved and the degree of tissue depletion can be readily calculated It has been found that the flat curves reflect marked tissue deficits The tissue deficits ranged from 3 to 5 grams in 11 cases studied All showed a deficit of 3 grams or more, with an average of 3.7 grams This is the approximate degree of tissue depletion present in cases of clinical scurvy³ Of nine cases with medium rises all but one showed a deficit of 2 to 3 grams, with an average of 2.16 grams Cases which exhibited a high curve without excretion are nearer saturation In this group the average tissue deficit was 1.4 grams Thus, it is seen that

the degree of tissue depletion can be determined with considerable accuracy by finding the three hour plasma concentration after administering a standard test dose of vitamin C

The Significance of Low Plasma Ascorbic Acid Concentration. A comparison of the initial fasting plasma ascorbic acid concentration with the curves has been made to determine whether the fasting blood plasma level alone reflects the tissue depletion. This has been found to be so. Thus, of 34 cases with fasting plasma ascorbic acid values ranging from 0.0 to 0.1 mg per cent, 15 showed flat curves representing an average deficit of 3.7 grams and 13 showed medium curves representing an average deficit 2.16 grams. The remaining six cases exhibited high curves. In only two instances was there any considerable excretion of ascorbic acid. Thus, 80 per cent of cases with fasting vitamin C values below 0.1 mg per cent exhibited very considerable depletion of the vitamin C stores. A smaller number of cases with blood plasma ascorbic acid concentrations between 0.1 and 0.3 mg per cent are available for similar analyses. Twelve of 19 cases with such fasting blood plasma levels showed medium three hour rises after the test dose of ascorbic acid. Others were high. These data are shown graphically in figure 2. With few exceptions, cases with initial blood plasma values above 0.3 mg per cent were found to be near saturation and excreted from 50 to 300 mg of the ingested dose of ascorbic acid.*

Determination of the tissue deficit is of interest but of greater practical importance is the evaluation of the significance of this deficit. At the outset it may be said that none of the cases included in this investigation showed the classical clinical picture of scurvy. Because of our special interest in the possible rôle of vitamin C deficiency in rheumatoid arthritis⁵ many of the cases studied were suffering from this disease. Several others had other complaints. The objective clinical criteria for diagnosis of mild or subclinical scurvy are few. A moderately extensive and somewhat contradictory literature revolves around the significance of capillary resistance tests. So

*These values represent the true concentration after subtraction of the ascorbic acid equivalency of the dye used in developing the end point in a blank. Naturally it is necessary that the titration be done carefully by an experienced technician with avoidance of the various factors that might give false values. We have used a modification of the original Farmer and Abt⁴ method as follows. 5 to 6 c.c. of fasting blood are collected in a test tube containing dry powdered sodium oxalate. The blood is centrifuged, and 2 c.c. of the clear plasma are placed in a centrifuge tube. To it are added 4 c.c. of distilled water and 2 c.c. of 5 per cent sodium tungstate followed by 2 c.c. of N/3 sulfuric acid. After thorough mixing the tube is allowed to stand for one to two minutes, then centrifuged. Two cubic centimeter portions of the supernatant fluid are pipetted into conical shaped centrifuge tubes and titrated with a dilute dye solution to the first faint pink color which remains for approximately 30 seconds. A microburette graduated in 0.01 or 0.02 c.c. is used for measuring the dye solution.

A stock dye solution is prepared by dissolving 50 mg. of 2,6 dichlorophenolindophenol in 100 c.c. of hot water, cooling, restoring the volume to 100 c.c., and filtering. If a pinch of sodium bicarbonate is added it improves the keeping quality of the dye solution. The stock dye solution is kept in the refrigerator and is good for about three weeks. It is standardized frequently against pure crystalline ascorbic acid. The stock dye is usually found to have an ascorbic acid equivalency of 0.2 to 0.25 mg. per c.c. To prepare the dilute dye for use in titration, one volume of the stock dye is diluted accurately with 19 volumes of water to give a dilution of 1/20. The resulting dye solution will have a value in terms of A.A. of 0.01 to 0.0125 mg. per c.c.

many factors may contribute to a lowered capillary strength that taken alone the test is of little value in detection of subclinical scurvy. It is not the purpose of this paper to review this controversy. There is, however, general agreement that although the capillary strength is reduced in many other conditions than vitamin C deficiency it is usually, though not invariably, also reduced in this condition. If a clearly reduced capillary strength can be ele-

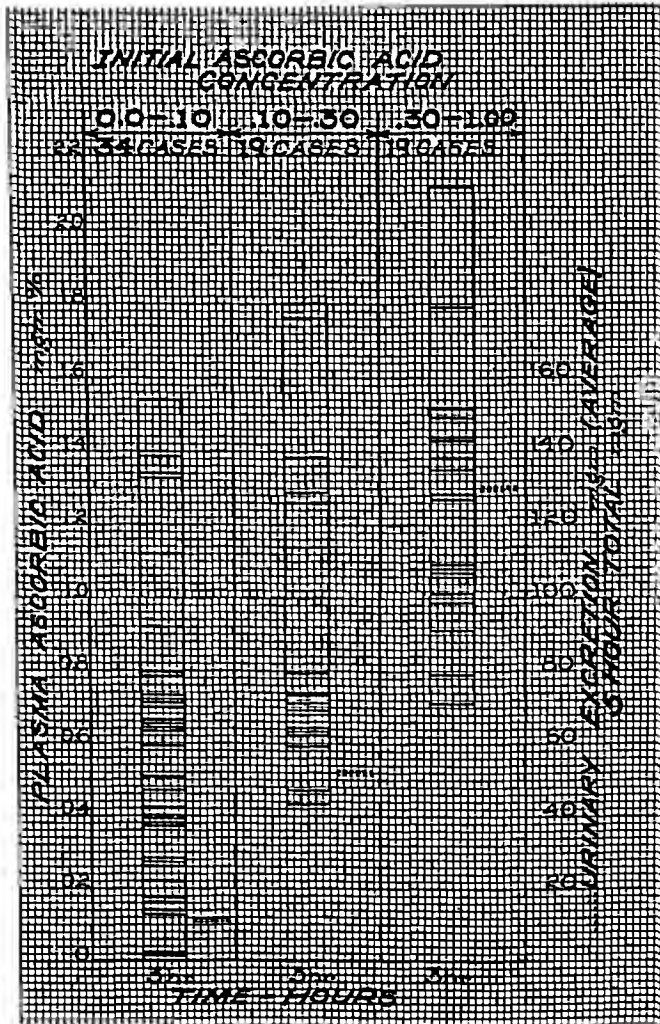


FIG 2 Showing two and a half to three hour level of plasma ascorbic acid after test doses of ascorbic acid of 15 mg per kilogram. Each cross bar represents the peak level of an individual case in the concentration range indicated.

vated by the simple administration of vitamin C, it may be considered valid evidence that vitamin C deficiency was the basis of the reduced capillary strength.

In determination of the capillary resistance we have used the instrument of Dalldorf⁶ in which controlled suction tension is applied to the skin through a standard glass cup. Because the capillary strength varies in dif-

ferent skin areas, it is essential that the same skin area be used in making comparative tests. In this study we have used the outer aspect of the upper arm (vaccination area). The skin surface is thinly smeared with vaseline and inspected under good light for preëxisting petechiae or confusing marks by pressing a glass slide against the area to be tested. The glass cup is then applied to this area; the desired suction tension is made and maintained by closing the valve leading from the pump. The suction is applied for a standard interval of one minute and then released by opening the valve. The area beneath the cup is again inspected for the presence of petechiae through a glass slide pressed against the skin and the number of petechiae is counted. The capillary strength then can be expressed in terms of the negative tension and the number of petechiae resulting, thus — 20/10 would indicate that 10 petechiae resulted from a negative tension of 20 cm. of mercury applied for one minute.

As in most subclinical deficiency states the effect on the general health and well-being of the patient following correction of the deficiency is perhaps the clearest evidence that deficiency existed.

On analysis of this series of cases in which five hour blood studies have been made, it is clear that a high percentage of those with fasting ascorbic acid concentration below 0.1 mg. per cent were suffering from the effects of inadequate vitamin C intake even though none of the cases presented a clinical picture that would be classified as scurvy by the usual criteria. Of 27 cases studied, 19 showed a lowered capillary strength. Thirteen of 16 cases which were followed after administration of vitamin C showed an elevation of the capillary strength. This elevation was apparent usually within two weeks. Seventeen of 22 cases followed after administration of vitamin C showed definite clinical improvement. Increased energy, loss of fatigability, and improved appetite were prominent clinical effects. As previously noted, many of the persons studied had rheumatoid arthritis. Improvement of the arthritis in varying degrees was noted in many cases. These observations will be reported subsequently in greater detail in a large series of cases. Reticulocyte counts were made in 10 of the cases. In seven there was a definite though mild reticulocytic rise following administration of vitamin C. This occurred even though the anemia present may have been mild. Twenty-three of 27 cases with initial plasma vitamin C concentration below 0.1 mg. per cent showed one or more of the effects noted after correction of the vitamin C deficiency. It is evident from this analysis that approximately 80 per cent of the cases in this series in which the initial fasting blood plasma ascorbic acid was below 0.1 mg. per cent were suffering from a subclinical form of vitamin C deficiency.

Observations on cases with fasting plasma ascorbic acid concentrations ranging between 0.1 and 0.3 mg. per cent are too few to be conclusive although it is clear that many had considerable tissue deficits and at least some of this group were suffering from effects of vitamin C deficiency. Several individuals in this group were known to have been taking fair amounts of

vitamin C, and it is probable that they had some fault in absorption of the vitamin. The cases in which the fasting plasma ascorbic acid concentration was above 0.3 mg per cent showed little tissue depletion, and it seems unlikely that they suffered significant deficiency.

The cases abstracted below illustrate the observations upon which this study is based.

A R, female, aged 23, complained of mild gingivo-stomatitis with small pharyngeal ulcers which bled. Initial plasma ascorbic acid was 0.02 mg per cent. Curve following test dose of ascorbic acid (15 mg/kilo) showed a medium rise to 0.78 mg per cent. No excretion. Deficit approximately 2 grams. Initial capillary resistance —20/40. Elevation of capillary resistance to —20/12 in three days. Slight reticulocyte rise. Healing of pharyngeal ulcers.

W K, male, aged 57. Diagnosis: Mild rheumatoid arthritis with slight swelling and stiffness of metacarpophalangeal and interphalangeal joints and soreness in knees and shoulders. Initial plasma ascorbic acid 0.0. Curve following test dose of ascorbic acid very flat, three hour peak, 0.13 mg per cent. Deficit 3 grams. Initial capillary resistance —15/90. Elevated to —16/8 in six days. Very mild reticulocyte response. Two months later general health and arthritis greatly improved.

T R, male, aged 33, complained of paresthesia of both hands in ulnar nerve distribution. Fasting plasma ascorbic acid 0.0. Curve following test dose of ascorbic acid flat. Three hour peak, 0.4 mg per cent. Deficit 3 grams. Initial capillary resistance —20/50. Increased to —20/12 ten days after administration of ascorbic acid. Paresthesias relieved.

M M, male, aged 31. Diagnosis: Rheumatoid arthritis of the spine. Initial plasma ascorbic acid level 0.0 mg per cent. Curve following test dose of ascorbic acid very flat. Three hour level 0.17 mg per cent. Deficit 4 grams. Questionable slight rise in capillary resistance from —16/4 to —20/1 after 21 days. No reticulocyte studies. Improvement in general health, sleeps better, less back pain.

W H, male, aged 38. Diagnosis: Rheumatoid arthritis of the spine. Initial plasma ascorbic acid 0.0 mg per cent. Curve following test dose of ascorbic acid (15 mg/kilo) medium rise to peak of 0.6 mg per cent. Tissue deficit 2 to 3 grams. Capillary resistance rose from —15/6 to —20/6 in 60 days. Increased energy and appetite. Less pain and increased movement in spine. Clear cut slowing of sedimentation rate.

E L, female, aged 30. Diagnosis: Mild rheumatoid type of arthritis. Initial plasma ascorbic acid 0.28 mg per cent. Curve medium rise to 0.68 mg per cent. Five hour level higher. No excretion. Second curve three hour level 1.28 mg per cent. No excretion. Deficit 2.5 grams. Capillary resistance normal. No reticulocyte rise. Marked symptomatic improvement in general health and arthritis. Diet history good. Probable absorptive fault.

Incidence of Subclinical Scurvy. We have seen that in the adult the severely lowered plasma ascorbic acid levels afford strong presumptive evidence of clinically significant vitamin C deficiency.

An analysis of data concerned with blood plasma values in 'health' and disease will be the subject of a subsequent report. It may be said, however, that vitamin C deficiency of the type described is frequently encountered. In a group of 239 'normals' consisting of students, nurses, house officers and laboratory workers 4.6 per cent showed fasting blood plasma levels below 0.1 mg per cent and 1.6 per cent were below 0.3 mg per cent. In

various diseases we have found the incidence of vitamin C depletion much higher. These findings correspond to the observations of Wright⁷ that clinically significant vitamin C deficiency is common.

DISCUSSION

The daily requirement for vitamin C has not been established with certainty. Rall, Friedman and Sherry⁸ have shown that the adult requires approximately 100 mg per day to maintain the blood in a state of saturation, i.e., at or above 1 mg per cent. Whether or not a lesser amount of ascorbic acid suffices for normal metabolism has not been established. The observations of Rall et al suggest, however, that a plasma ascorbic acid level in the vicinity of 0.5 mg per cent may be maintained with an intake of 50 to 75 mg a day. We have shown that tissue depletion of persons with blood concentrations in this range is minimal. It would appear unwise at present to consider plasma concentrations above 0.3 mg per cent (0.3 to 0.8 mg per cent) as indicating deficiency even though they do not reflect saturation.

The experiments of prolonged acute vitamin C deprivation in man are of interest but must be properly evaluated. Schick⁹ deprived himself of vitamin C containing foods for a period of 160 days without showing any clear-cut evidence of vitamin C deficiency. Crandon⁴ subjected himself to vitamin C deficiency for six months and except for fatigability at three months and gradual weight loss, no evidence of deficiency was manifest during the first four months. At 132 days hyperkeratotic skin papules appeared, and perifollicular hemorrhages were first evident in 161 days. It is of interest that the tissue deficit in each case was approximately 4 grams. This probably represents the approximate total vitamin C stores in the human adult. In the Crandon experiment, it should be remembered that all other vitamins were supplied in excess and that the vitamin C stores were good at the outset of the experiment and presumably had been so in the past. In clinical medicine very different circumstances prevail. From analysis of dietary histories, evidence is clear that many of the subjects of this study had been taking minimal amounts of vitamin C for years. Absolute lack of vitamin C is uncommon, but it appears that practically complete deprivation of ascorbic acid is necessary for the development of the picture which we recognize as classical clinical scurvy. On the other hand, long standing sub-optimal intake is much more common. It is probably the chronic deficiency that we have recognized in the study. The designation of chronic scurvy might be more appropriate than the term subclinical.

Observations of Kramer¹⁰ and Roff and Glazebrook¹¹ are worthy of note. Kramer studied 34 soldiers in the German air force who were suffering with gingivitis and stomatitis. He found the average ascorbic acid tissue deficit to be 2 to 2.5 grams, and treatment with ascorbic acid effected a cure in each case except one. In addition to the local oral pathologic lesions fatigue, leg pain and anorexia were very prominent symptoms which

were also relieved by administration of vitamin C. This is in accord with our own observations. Roff and Glazebrook described cases of gingivostomatitis among boys in a training establishment of the Royal Navy. The gums were congested and spongy, the surfaces having a gelatinous feel. Bleeding did not occur on simple palpation, but if one pierced with a probe the hemorrhage was more copious than usual. The congestion was uniform, from the gums into the sulci on to the buccal mucous membrane, extending backwards and involving the tonsils and pharyngeal wall as far as the eye could see. In all cases vitamin C deficiency was found with an average ascorbic acid deficit of approximately 4 grams. The condition responded to administration of ascorbic acid. These authors also recorded prominent symptoms of lassitude and rheumatic pain in and around the larger joints. They note that exactly similar symptoms occur in cases in which there is evidence of infection, and that such cases may later develop rheumatic fever, with true arthritis, or carditis may develop silently without further manifestations of rheumatism. They note "It is often impossible to differentiate from the description of the symptoms of the patient a case which will clear up on saturation with vitamin C, from one which will tend to progress to rheumatism and carditis." They further found that the highest incidence of scorbutic gingivostomatitis and of rheumatic fever fell upon recruits from a given area in which the economic conditions were below standard for the country as a whole.

Various hemorrhagic manifestations may be encountered in vitamin C deficiency. In cases of unexplained purpura or other bleeding, vitamin C deficiency should be considered as a possible major or contributory factor. Although many cases will be found to be dependent upon other factors a determination of the fasting plasma ascorbic acid is indicated in such cases.

SUMMARY

Determination of the fasting plasma ascorbic acid is the simplest, most direct exploratory method in detection of subclinical vitamin C deficiency or scurvy. A simple method for determination of the degree of tissue depletion is presented. This is based upon the rise in the plasma ascorbic acid following a standard peroral test dose of ascorbic acid (15 mg/kg). Flat curves reflect severe tissue depletion, medium curves, moderate depletion. Eighty per cent of cases with fasting blood plasma levels below 0.1 mg per cent showed marked or moderate tissue deficits of ascorbic acid which ranged from 2 to 5 grams. In approximately 80 per cent of cases with fasting plasma ascorbic acid levels below 0.1 mg per cent, demonstrable improvement followed administration of vitamin C. Thus, concentrations in this range afford strong presumptive evidence of subclinical scurvy. Fasting plasma vitamin C values between 0.1 and 0.3 mg per cent are probably indicative of significant deficiency in a smaller percentage of cases, but data in the group are not adequate for judgment. Cases with plasma ascorbic acid

levels ranging from 0.3 to 0.8 mg per cent show only mild tissue depletion, and it appears unlikely that they are suffering from vitamin C deficiency even though the tissues are not saturated.

Objective criteria for detection of vitamin C deficiency are few. A lowered capillary strength per se is of little value as an index of such deficiency. However, a lowered capillary strength that is elevated by administration of ascorbic acid is acceptable evidence of preexisting vitamin C deficiency. Mild reticulocyte responses following administration of vitamin C may prove a useful objective index of deficiency. This should be studied further. General symptoms of lassitude, fatigability, anorexia and rheumatic pains are frequent in the presence of vitamin C deficiency. Gingivitis and gingivo-stomatitis occur commonly enough to arouse the suspicion of hypovitaminosis C. Vitamin C deficiency should be considered as a major or contributory factor in cases of unexplained bleeding. Unpublished observations indicate that vitamin C deficiency or subclinical scurvy of the type described is commonly encountered in medical practice.

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CORONARY OCCLUSION; A CLINICAL STUDY OF 100 PATIENTS *

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As the diagnosis of coronary occlusion has become more and more precise, many clinical and pathological studies of patients with this disease have been added to the literature. Master, Dack and Jaffe¹ have recently reported a study of 500 patients with coronary occlusion seen at the Mount Sinai Hospital and have adequately reviewed the entire literature on this subject. Their bibliography includes the clinical reports of 2,803 patients with this disease and necropsy studies in 1,241 other patients with coronary occlusion. This recent complete review obviates the necessity for another detailed survey of the literature.

MATERIAL

Since 1930, 100 private patients with coronary occlusion have been studied by us. Seventeen of the series were referred by other physicians, and their clinical courses were followed through the referring physician.

TABLE I
Sex, Age Incidence and Subsequent Clinical Course

		In 100 Patients Male 85 Female 15					
		Well	Sick		Dead		
		54	12		34		
Clinical Course of Different Age Groups in Decades							
Youngest patient 28 years of age Oldest patient 78 years of age							
Decade	20-30	30-40	40-50	50-60	60-70	70-80	Total
Living	0	3	17	30	10	6	66
Dead	1	1	7	10	13	2	34

Mortality Rates

Immediate mortality (within 21 days)	12
Subsequent mortality	22
Total mortality	34

Sex, Age, Incidence, and Subsequent Clinical Course (Table 1) Fifteen patients in our series of 100 were females. This is a ratio of 66:1, and was considerably lower than the 3:1 ratio of the entire literature. The ratio range in all clinical cases reported in the literature was between 3:1

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and 13.1. This, then, is a reasonable average when compared with those previously reported.

Age Distribution (Table 1). This did not vary materially in our series from those previously reported. Our youngest patient was 28 years old, and the oldest was 78 years old. Five per cent of our patients were less than 40 years of age. In the series of Master et al.,¹ 78 per cent were below 40. Except for a slightly greater number of patients occurring in the sixth decade, our age distribution was quite similar to previously reported studies. Peak incidence was definitely shown to belong to the sixth decade, 40 per cent of the patients falling in this age level.

Mortality Rate (Table 1). There was an immediate (within 21 days) mortality of 12 per cent and a total (immediate and subsequent) mortality of 34 per cent in this series. Sixteen patients died in subsequent attacks of coronary occlusion, four died of subsequent congestive heart failure, and two died of causes unrelated to cardiac disease. The mortality rates of different decades remained practically constant except in those between the ages of 60 and 70. Here was found more than a 20 per cent increase in the average 34 per cent mortality for the group. From previously reported studies the mortality rate of patients in the second and third decades was definitely less than in the older groups. This was not apparent in our series, and was probably due to the small number of patients in this age group. Our mortality rate in women was two out of 15 (13.3 per cent). This was much less than the average mortality rate for the entire group and differs from the majority of studies reported by other workers.^{2,3,4} The higher mortality in women has been attributed to the greater incidence of diabetes. In our series only two of the 15 women were diabetics and both of these patients are living and well.

TABLE II

Length of Observation

In 66 Patients Who Recovered from Coronary Occlusion

3 years or less	36
3 to 6 years	17
6 to 9 years	12
Over 9 years (23 years)	1

Length of Observation (Table 2). In 66 patients who have survived the initial attack of coronary occlusion, 36 have been followed three years or less, 17 were studied from three to six years, and 12 were studied from six to nine years. The oldest individual in the group has been followed by one of us for 23 years. He is now living and well.

Length of Life After the Initial Attack in 34 Patients with Fatal Coronary Occlusion (Table 3). Of this group, 13 died in less than 21 days after the initial attack, 10 others died within 10 months after the initial attack, and of the remaining 11, 10 died within 28 months after the initial

TABLE III
Length of Life After Attack
In 34 Patients With Fatal Coronary Occlusion

Less than 24 hours	4
Less than 7 days	5
Less than 14 days	1
Less than 21 days	3
Less than 28 days	2
Less than 2 months	4
Less than 3 months	4
Less than 5 months	1
Less than 9 months	1
Less than 20 months	3
Less than 28 months	5
6 years and 2 months	1

attack One patient lived six years and two months, only to die of chronic congestive heart failure

Recurrent Coronary Occlusion and the Time After the Initial Attack
(Table 4) Twenty-five per cent of the patients in this study had recurrent

TABLE IV
Recurrent Coronary Thrombosis and Time After Initial Attacks
100 Patients

Fatal 2nd Attack 15 Patients	Fatal 3rd Attack 1 Patient	Non fatal 2nd Attack 5 Patients	Non-fatal 3rd Attack 4 Patients
6 days	6 years, 2 months	2 months	9 months
7 days		3 months	10 months
14 days		4 months	18 months
17 days		17 months	18 months
21 days		38 months	
4 weeks			
6 weeks			
7 weeks			
3 months			
3 months			
5 months			
5 months			
1 year			
1 year			
2 years, 6 months			

attacks of coronary thrombosis In all but three patients the recurrent attacks came within two years after the initial attack Fifteen of the 25 patients died in the subsequent attacks This mortality rate of 60 per cent is almost double that of the initial attacks (34 per cent)

Occupation and Race (Table 5) As has been previously demonstrated,⁵ coronary occlusion occurs more often in the higher orders of intellect of the Caucasian race Those engaged in professional occupations or positions of responsibility are most often victims of the disease In this series, 67 per cent were business men of the executive type, or those engaged in small businesses requiring much individual effort and initiative The frequent occurrence among traveling men is of interest This suggests the vulnerability of those who work hard and participate in irregular living and habit

TABLE V
Occupation and Race
In 100 Patients With Coronary Occlusion

Business men	30
Business executives	23
Traveling salesman	14
Physicians	10
Lawyers	4
Interior decorator	2
Night watchman	2
R. R. engineer	1
Farmer	1

Race Distribution

All White

Gentile	Hebrew
90	10

excesses Ten per cent of the patients in this group were physicians This probably represents the highest "occupational per cent" found in the series

Habit Excesses (Table 6) An attempt was made to evaluate habit excesses that might in some way be responsible for the development of this

TABLE VI
Habit Excesses
In 100 Patients With Coronary Occlusion

Eating	32
Smoking (12 did not smoke at all)	17
Liquor	11
Worry	25
Work	41
No bad habits	3
Data insufficient	22

disease Excess work, largely mental, was found in 41 per cent and was the most common over-indulgence Over-eating came next and was found in 32 per cent Excess worry came third, being found in 25 per cent Nicotine played an inconclusive part Seventeen per cent over-smoked, but 12 per cent did not use tobacco at all Liquor, as has been shown before,⁶ plays little if any part in the production of coronary occlusion Eleven of the group were excessive drinkers, but in no instance did the attack occur during an alcoholic bout In many patients, whiskey was used to advantage in controlling attacks of anginal pain

The combination of over-eating, over-working, and excess worry seems to form the most potent combination of the etiologic factors

Diseases (Other Than Vascular) Associated with Coronary Occlusion (Table 7) In 51 of these patients no disease other than that of the vascular tree was found As evidence of the previously discussed excess eating habit, obesity was common and occurred in 35 of the 100 patients Malnutrition was quite uncommon and occurred in only 4 per cent of the group

TABLE VII
Diseases Associated With Coronary Occlusion
In 100 Patients

Obesity	35
Malnutrition	4
Diabetes mellitus	8
Chronic cholecystitis	9
Abscessed teeth or tonsils	3
Chronic bronchitis	9
None detected	38

Diabetes mellitus was found eight times, this frequency being slightly less than that described in other studies. Master et al.¹ found 11.2 per cent in their series of 500 patients (mostly Jewish). Conner and Holt⁷ found about 11 per cent diabetics in a series drawn largely from gentiles. All but one of our diabetics was more than 50 years of age, and none was less than 45 years of age. The sexes were equally divided in the diabetics of the series. In those reported in the literature,¹ diabetes was four times more frequent in women.

Chronic cholecystitis was found nine times in the 100 patients. In one patient, coronary occlusion followed cholecystectomy. In four patients oral infections (abscessed teeth or tonsils) seemed closely associated with the acute onset of coronary thrombosis. Removal of abscessed teeth was followed by coronary occlusion in three patients. Only two patients in the entire group had the acute attacks of coronary occlusion precipitated by operation—one cholecystectomy and one prostatectomy. In a previously reported study⁸ 5.6 per cent of 625 patients with coronary occlusion developed the attack after major surgical procedures. In three patients with chronic bronchitis, coughing paroxysms may have been associated with the acute coronary thrombosis.

TABLE VIII
Events Associated With Immediate Attacks
In 100 Patients With Coronary Occlusion

Physical exertion	32
While in bed	10
During or immediately after a meal	5
Severe emotional upset	4
Major surgery (prostatectomy-cholecystectomy)	2
Insufficient data	47

Events Associated with the Immediate Attack (Table 8). In 49 patients no significant event could be associated with the immediate attack. In 32 of the remaining 51 patients physical exertion of varying degrees was associated with the onset of the acute attack. Ten patients, however, had the acute attack while in bed. This may have been associated with a slowed blood flow occasioned by bed rest. In five patients coronary occlusion occurred after a large meal. A severe emotional upset seemed to precipitate the attack in four patients.

From an analysis of the events associated with the immediate attack, it seems that an increased circulatory load is the precipitating factor in the majority of the patients, but in 19.6 per cent (10 of 51) the acute coronary closure occurred in a resting state and was probably associated with a slowed blood flow

TABLE IX
Complications Associated With Immediate Attack
In 100 Patients With Coronary Occlusion

Circulatory collapse	31
Cerebral embolism	5
Pulmonary embolism	3
Popliteal embolism	2
Renal suppression (fatal)	1
Psychosis	3
Pleural effusion	2
None	53

Complications Associated with the Immediate Attack (Table 9) Circulatory collapse complicated the immediate attack in 31 patients. This was a grave prognostic sign, and 21 of these 31 patients died.

Embolic phenomena occurred in 10 per cent of our patients. In a previously reported study⁹ embolic phenomena were found in 14 per cent of all patients with cardiac infarction. Occasionally embolic phenomena occur as the only symptom of a recent coronary occlusion. History and electrocardiogram will usually reveal the occurrence of the cardiac infarction which has been responsible for the embolus.

Psychoses that were transient occurred in 3 per cent of the series.

Fatal renal suppression following circulatory collapse was encountered once.

In 53 of the 100 patients, no complications were associated with the immediate attack. The mortality rate in this group was considerably lower than that for the entire group.

The Occurrence of Angina Pectoris Before and After Coronary Occlusion (Table 10) Thirty-three patients of the group had angina pectoris

TABLE X
Angina Pectoris
Before and After Coronary Occlusion in 100 Patients

Previous and subsequent angina	33
No previous but subsequent angina	23
Previous but no subsequent angina	13
No angina before or after coronary occlusion	15
Indefinite history as to previous or subsequent angina	6
Previous angina in 12 who died in the immediate attack	10

both before and after coronary occlusion occurred. In many instances, however, the degree of angina was less after the attack of coronary occlusion. Twenty-three patients denied having angina previous to the attack of coronary occlusion, but complained of it as a post-occlusion symptom. In

13 patients angina disappeared after coronary occlusion occurred. Fifteen patients denied cardiac pain either before or after the acute attack. It was possible, however, to get from some in this group symptoms of palpitation, shortness of breath, and substernal oppression.

TABLE XI
Referred Pain and Abdominal Distress
In 100 Patients With Coronary Occlusion

Epigastrium	14
Elbows or arms	22
Shoulders	4
Cervical vertebrae	2
Lumbar vertebrae	1
None (all pain substernal or precordial)	23
Data insufficient	34
Abdominal distress	50

Referred Pain and Abdominal Distress (Table 11) Many observers have pointed out the areas to which coronary pain may be referred. A knowledge of these is important to a correct differential diagnosis. Herrick,¹⁰ in 1935, listed 28 different diseases that were diagnosed as coronary occlusion. These 28 diseases illustrated practically all points of referred pain.

An analysis of the referred pain in 46 patients of the group shows it to have occurred in practically all points that have previously been described. The epigastrium and upper extremities were the most frequent sites of pain referred. In 23 patients no history of any referred pain could be elicited. Abdominal fullness and epigastric distress occurred in slightly more than half of the patients, and was in some the most difficult of all symptoms to control.

Blood Pressure Studies Before and After Coronary Occlusion (Table 12) In previous studies hypertension has been found in 33 to 73 per cent of patients as an antecedent to coronary occlusion. Levine's series¹¹ showed

TABLE XII
Blood Pressure Studies Before and After Coronary Occlusion
In 100 Patients

Before Attack		After Attack	
High	to	High	18
High	to	Normal	7
High	to	Low	16
Normal	to	High	2
Normal	to	Normal	27
Normal	to	Low	19
Low	to	High	0
Low	to	Normal	0
Low	to	Low	9
Insufficient data			2

Summary of Blood Pressure Findings

Before Attack			After Attack		
High	Normal	Low	High	Normal	Low
41	48	9	20	34	44

40 per cent hypertensive. In the series by Master et al,¹ 62.4 per cent of their patients had an antecedent hypertension. They thought that even this figure was lower than the actual incidence. In our series 41 of the 100 patients were known to have had a previously existing hypertension. Hypertension persisted in only 18 patients after coronary occlusion. Normal or low blood pressure after the attack of coronary occlusion was found in 78 per cent. This reduction in pressure persisted in many for months, or even years, following the coronary occlusion.

Of the 59 patients with normal or low blood pressures antedating the coronary occlusion, only two were abnormally high after the attack.

In this study there was no demonstrable connection between mortality rate and previously existing hypertension. The incidence of hypertension in women with coronary occlusion has been shown to be¹ 32 per cent higher than that found in men. This finding was corroborated in our series.

TABLE XIII
Cardiac Hypertrophy and Degree of Arteriosclerosis
In 100 Patients With Coronary Occlusion

Cardiac Hypertrophy (found in 59 patients)				
None Found	One Plus	Two Plus	Three Plus	Four Plus
41	19	31	8	1
Arteriosclerosis (found in 97 patients)				
None Found	One Plus	Two Plus	Three Plus	Four Plus
3	33	43	20	1

Cardiac Hypertrophy (Table 13). Enlargement of the heart was found in 59 per cent of our patients. Progressive cardiac hypertrophy was observed in 10 per cent of the patients following cardiac infarction. In this series the relation of hypertrophy and hypertension was not clear, but there was a very definite parallel between cardiac hypertrophy and mortality rate. Both immediate and subsequent mortality was materially increased in those with cardiac hypertrophy.

Arteriosclerosis. Some degree of arteriosclerosis could be demonstrated in 79 per cent of our patients. In the majority (76 per cent) it was not marked in the large palpable vessels. There was little demonstrable relationship between the degree of peripheral arteriosclerosis and the mortality of coronary occlusion. This would indicate that the degree of arteriosclerosis or atherosclerosis present in the coronary arteries could not be determined from that manifested in peripheral vessels.

COMMENT

After studying this group of patients and those of other workers, we are left with an attempt to answer such questions as these. Why do certain

individuals have coronary occlusion whereas others with even more evident vascular pathology do not? Why do certain patients recover from the attack and others either die immediately or of subsequent cardiac failure? Why will some die suddenly without history of previous coronary insufficiency and with a normal electrocardiogram? What habit excesses in our modern method of living are responsible for the apparent increase in the disease? In one that is a coronary suspect, what things should be done or avoided in order to prevent the development of an acute coronary closure? And last, but of considerable importance, what is best to do for a patient after coronary thrombosis has developed?

Complete answers to these questions are not yet available, but our increasing knowledge from continued study does throw light on some. That the disease is more prevalent in the higher orders of intelligence is evident. Those occupying positions of responsibility are most often victims. The colored race, even though quite emotional, have very little of the disease. It has been found in only 14 patients (63 per cent) of 2,204 cardiac patients of all types studied at the Colored Grady Hospital during the past 10 years. This low incidence is further substantiated by postmortem examinations. In the White Grady Hospital coronary occlusion occurred in 3.4 per cent (17 of 496 patients in 1938) of all cardiac patients. In this series of private office and hospital patients the frequency of coronary thrombosis compared to all other types of heart disease was approximately 10 per cent. The prevalence of hypertension and arteriosclerotic disease in the colored race is well known and undoubtedly exceeds that found in the white race, especially in the third and fourth decades. Yet they are almost immune from coronary occlusion. This leads one to the conclusion that the added factor of a high-tensioned sympathetic nervous system and an exaggerated sense of responsibility are a combination that in some way produce the disease regardless of the degree of generalized vascular disease and hypertension that exists.

A consideration of why some patients die of coronary thrombosis whereas others recover seems to revolve principally around the rate of speed with which the coronary occlusion occurs, and the degree of underlying coronary artery and myocardial disease that is already present at the time of the acute closure. Those who have a minimal amount of co-existing myocardial and coronary disease and who occlude gradually so that time is allowed for the establishment of a collateral circulation apparently have the best prognosis, both as to mortality and morbidity. Those who have considerable preëxisting myocardial and coronary disease and who experience rapid closure of the coronary artery stand less chance of recovery.

Early diagnoses and proper treatment of the immediate attack should materially reduce morbidity and mortality rates. In a patient with suspected coronary occlusion, absolute bed rest should be maintained until the true diagnosis is established. Two or more electrocardiograms should be

made during this period of observation. Often an interval of five to seven days is necessary before the electrocardiogram will confirm or disprove the suspected diagnosis. Occasionally, longer periods of observation are necessary. In this series one patient did not show positive electrocardiographic changes until 15 days had elapsed, and in another characteristic changes were not found until the fifth week. The finding of a leukocytosis and an increased sedimentation rate often help in establishing a correct diagnosis.

TREATMENT

After a definite diagnosis is established the following treatment should be carried out.

Complete bed rest should be strictly enforced during the critical 21 day post-occlusion period. Modifications as to the amount of bed activity during this time would be determined by the severity of the attack. For the milder attack four to six weeks of bed rest should be enforced. For the more severe attacks eight to 10 weeks of complete bed rest are necessary. Convalescence should be gradual and should be systematically planned.

Relief of pain is of paramount importance. Opiates will be necessary in the more severe attacks. Extreme caution should be exercised in the effort to prevent nausea and vomiting from opiates. This complication alone may precipitate a fatal ventricular rupture, ventricular fibrillation, or embolus formation.

The combined use of opiates with sodium luminal, aminophyllin by vein or rectal administration, and oxygen inhalations will often relieve pain without producing nausea, and less opiate is required than if opiates alone are used. Small doses of whiskey have a vasodilating and pain relieving effect. Diathermy over the precordium is of questionable value in relieving residual anginal pain after healing has occurred. Diathermy should not be used during the healing period.

The relief of dyspnea is most satisfactorily effected by continuous oxygen inhalations. Rectal or intravenous injection of aminophyllin will often give great relief from the orthopnea and dyspnea of acute left ventricular failure.

The care of the gastrointestinal tract is important. Gaseous distention should be prevented by small frequent feedings of liquid and soft diet. Dextrose given in water at two hour intervals is helpful. Occasionally, it will be necessary to give fluids and dextrose by hypodermoclysis. Fluids should never be given by venoclysis.

Small doses of laxatives given frequently will often help prevent abdominal distention. Heat applied to the abdomen is of value. Prostigmin or pitressin should not be used to combat flatulence.

Small enema of oil and glycerin (six to eight ounces) should be used exclusively rather than the usual 2 liter enema of saline. The larger enemas may, by their exhausting effect and the increased abdominal pressure, produce a fatal complication.

Cardiac Medication Quinidine sulfate in three to five grain doses at three hour intervals may prevent the occurrence of disastrous arrhythmias (auricular fibrillation, flutter, or ventricular fibrillation)

Coramine, by hypodermic, should be cautiously used Although it has been shown to produce an increased coronary blood flow, the elevation of blood pressure associated with its hypodermic use is not desirable in the acute phase of a coronary thrombosis

Atropine sulfate is of questionable value Some workers have claimed an increased coronary flow due to the increased heart rate caused by vagal release

Digitalis is definitely contraindicated in acute coronary thrombosis unless the patient has developed congestive heart failure or auricular fibrillation with a rapid ventricular rate With either of these complications it should be cautiously used

Other circulatory stimulants such as adrenalin, caffeine, and strophanthin should be avoided entirely unless the degree of circulatory shock demands their use Even then, small doses cautiously used may be enough to overstimulate the ventricle and produce a fatal complication Glycocol has been used by some to relieve the extreme exhaustion that develops in severe attacks

SUMMARY

1 One hundred white patients with coronary occlusion are reported This includes consecutive patients seen and followed in private practice since 1930

2 There was an immediate mortality of 12 per cent and a total mortality of 34 per cent

3 Twenty-five of these patients had subsequent second or third attacks of coronary thrombosis

4 Occupations involving executive capacities or considerable individual initiative were most frequent

5 Overworry, overwork, and overeating were the most commonly occurring habit excesses

6 Obesity, chronic cholecystitis, and diabetes mellitus were the most commonly associated diseases

7 Physical exertion, bed rest, large meals, and emotional upsets were the most frequent events associated with the immediate attack

8 Circulatory collapse and embolic phenomena were the most common complications of the immediate attack

9 Angina pectoris, before and after the attack of coronary occlusion, was more common than no angina before or after the attack

10 Referred pain was most common in the upper extremities and epigastrium, but was found in all levels from the mastoids to the lumbar region Abdominal distress occurred in 50 per cent

11 Hypertension before the attack was found in 41 per cent, and it persisted after the attack in 20 per cent

12 Cardiac hypertrophy either before or after the attack was found in 59 per cent Forty-one per cent had a normal sized heart Arteriosclerosis in varying degrees was present in 97 per cent

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PNEUMOCOCCAL MENINGITIS *

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INTRODUCTION

IN 1896 Jemma¹ reported one of the earliest if not the first case of cure of pneumococcal meningitis. In spite of frequent subsequent reports of cures in the literature, this disease for many years has been thought to be almost always fatal. Goldstein and Goldstein² made an exhaustive study of the literature in 1927 and reported that "there are on record in the literature about 150 cases of recovery from proved pneumococcal meningitis." The recent increase in the frequency of reports of cures seemed to justify a review of the literature and especially an evaluation of the various methods of therapy employed. These methods were carefully analyzed and evaluated in the hope of disclosing some common denominator which would give the clue to the successful treatment of this disease. This review and an analysis of the cases of pneumococcal meningitis seen at the Cincinnati General Hospital in the period from 1936 through 1941 form the basis of this report.

EXPERIMENTAL

Several investigators have succeeded in producing this disease in animals, and have thereby contributed considerably to our understanding of its human counterpart. Stewart,³ after discarding cats and rabbits, found the dog to be a suitable experimental animal. He succeeded in reproducing the disease in this animal by the intracisternal inoculation of virulent pneumococci. With Type I infections the picture presented was that of a rapidly spreading, fibrino-purulent leptomeningitis which involved all regions of the meninges as early as 24 hours after infection. In some animals, superficial encephalitis with invasion of the choroid plexuses was present, in others, the cord dura was invaded, the spinal nerve roots were involved, and there was an inflammatory process in the epidural fat. Especially remarkable, and important from the standpoint of treatment, was the high incidence of central cord involvement or even of suppurative myelitis in a large series of dogs infected with Type I pneumococci. In several instances this worker was able to effect cures by cisterno-lumbar lavage and the intrathecal introduction of an optochin-serum mixture. He thought it extremely important to bring

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all parts of the meninges into frequent contact with the therapeutic agent, when such contact was not complete "reinfection" was almost inevitable

Stewart's³ efforts with Type II infections were equally successful in reproducing the disease. He found, however, that Type II pneumococcal meningitis in dogs was characterized by the early production of a heavy fibrinous exudate and a consequent tendency toward the development of subarachnoid "blocks." The exudate tended to involve the walls and perivascular sheaths of deeply penetrating vessels, with subsequent parenchymatous softening and brain or cord abscesses. The lateral ventricles appeared to be a point of election, and hydrocephalus occurred early. Central myelitis was common and also appeared early in the disease. Employing a technic similar to that used in Type I infections, he was unable to effect any cures in canine Type II pneumococcal meningitis.

Kolmer and his associates⁴ produced meningitis experimentally in rabbits and treated the animals with intrathecal injections of ethylhydrocuprein alone, and in conjunction with the homologous serum. They were able to reduce the mortality only slightly even though treatment was begun a few hours after infection. They, too, discarded the rabbit and selected the dog as a more suitable animal for pneumococcal experimentation. Following their production of the disease in dogs, they employed various antiseptics and antibodies as therapeutic agents but found none to be of eminent value. They did feel, however, that the lavage of the ventricular system was effective and that this might be combined with intrathecal administration of specific antibody or ethylhydrocuprein. Later, they reported cures in animals following the intracarotid and intracisternal injection of a mixture of Huntoon's antibody and ethylhydrocuprein. More recently Kolmer^{1a} showed that sulfanilamide administered to these artificially infected animals prolonged their lives.

Gross and his collaborators^{5, 5a} have reported the production of pneumococcal meningitis in rats after the intracranial inoculation of broth cultures of pneumococci. The disease produced in these studies very closely resembled that produced in dogs. Encephalitis occurred in more than half of the untreated animals. Pus was found in the cerebral ventricles in two-thirds of the rats at necropsy. In these animals, too, pus in the central canal or frank myelitis was found very frequently, occurring in about 40 per cent of the untreated animals. These workers employed various forms of therapy including the sulfonamides as well as specific serum. They found both sulfanilamide and sulfapyridine to be effective in reducing the mortality in the experimental disease, in Type I infections a combination of sulfanilamide by mouth and serum intraperitoneally was the most effective treatment. Type III antipneumococcus serum was without effect in treating the homologous infection. Increasing the size of the infecting dose or delay in instituting treatment diminished the likelihood of recovery. It is interesting to note that the animals which recovered showed very little evidence of a previously existing meningitis.

DIAGNOSIS

The clinical picture of pneumococcal meningitis is not characteristic. If signs of meningitis supervene during the acute stage of pneumococcal pneumonia, the etiology of the former may be presumed to be pneumococcal. But pneumococcal invasion of the meninges does not produce either signs or symptoms which are pathognomonic.

The diagnosis of the disease should depend on an examination of the spinal fluid. The fluid is usually under increased pressure, in the majority of instances it lacks the usual transparency of normal spinal fluid, varying from a ground glass to a frankly purulent appearance. Further examination may show a decrease in the sugar content and an increase in protein and cellular elements. Almost always the predominant cell is the polymorphonuclear leukocyte, but Malaguzzi-Valeri⁶ reported a case of meningitis due to mouse-avirulent Type I pneumococci in which the cellular reaction of the cerebrospinal fluid was lymphocytic.

Rhoads et al.⁷ have rightly pointed out the error of the old dictum that meningitis is due to the meningococcus until proved otherwise. As with other bacterial diseases, the diagnosis of pneumococcal meningitis should depend on the demonstration of the organism. In more than half of the cases this can be done by a microscopic examination of the spinal fluid with the aid of suitable typing sera. If this fails, culture of the fluid will usually yield sufficient growth within a few hours to permit of the rapid identification of the organism. Identification of the pneumococcus by tinctorial methods has undoubtedly confused the picture of pneumococcal disease as reported in the literature, and should be deprecated. The finding of gram-positive organisms in pairs is not sufficient evidence for the diagnosis of pneumococcal meningitis, if such organisms are bile-soluble, the diagnosis may then be made. The adaptability of the "quellung" phenomenon of Neufeld has largely eliminated the necessity for bile-solubility determinations, and permits of a rapid species as well as type identification.

Any type of pneumococcus may cause meningitis. The so-called "higher" types of pneumococci are less likely to cause meningitis, but there is no reason to believe that these "higher" types are any less virulent after they have invaded the meninges. Table 1 will show the distribution of types of pneumococci causing meningitis in three large metropolitan hospitals in the United States, as compared with a large series reported by Ordman⁸ from South Africa. Close study of the table reveals that the type-distribution of pneumococci causing meningitis follows no pattern closely as it does in pneumonia. The one apparent exception is the high incidence of Type III pneumococci in the three American series, the high incidence of Type III pneumococcus in ear and sinus infections and the predisposing influence of such diseases probably explains this exception. Fuller and more accurate reporting of pneumococcal disease in the future may disclose incidences, the significance of which is not apparent from such small series. It may be

worth while to point out the disparity in per cent incidences of Type I pneumococcus between the United States and South Africa. In the latter country this organism occurred to about the same extent in pneumonia as it did in meningitis. In this country, Type I causes pneumonia in 20 to 30 per cent of many large series, whereas in the three listed series of meningitis it was the causative agent in no more than 6 per cent. The typical nature of Type I pneumococcal pneumonia and the early use of potent sera may be

TABLE I

This table contains the type variations in three large general hospitals in the United States as compared with the distribution as reported by Ordman in South Africa. The New York figures are taken from the Harlem Hospital, and were kindly furnished by Dr J. G. M. Bullowa. The Boston figures were reported from the Boston City Hospital by Dr Maxwell Finland.

Type	Cincinnati	New York	Boston	South Africa
I	3	4	6	113
II	12	2	10	28
III	10	14	18	30
IV	5	5	5	
V	8	2	6	25
VI	6	6	2	
VII	6	10	7	18
VIII	4	7	12	
IX	1	2	2	
X	1	3	5	4
XI	1	0	3	
XII	5	5	2	26
XIII	0	0	2	
XIV	3	8	4	9
XV	0	0	0	
XVI	0	0	0	
XVII	1	1	1	
XVIII	1	6	3	
XIX	2	1	2	
XX	1	3	3	
XXI	0	1	0	
XXII	2	1	1	
XXIII	1	7		
XXIV		0		
XXV		2	1	7
XXVII			1	
XXVIII	1		1	
Above XXXII	2	2	2	
Untyped			1	
	76	92	100	Others 433 697

responsible for the low incidence of this type of meningitis. The predominance of Type II and Type V pneumococci in the Cincinnati series is accounted for by the high incidence of endocarditis complicating pneumococcal pneumonia at the Cincinnati General Hospital, the frequency with which meningitis occurs as a terminal event in pneumococcal endocarditis has been reported previously.⁹

The infrequency with which more than one organism attacks any given part of the body at the same time is well exemplified in meningitis. This phenomenon is especially difficult to explain in meningitis which follows

head injuries and skull fractures During the years 1936 to 1941 at the Cincinnati General Hospital, more than one kind of organism was never found in an infected spinal fluid A rare instance of multiple infection is recorded in the literature Some confusion may be caused by cross-reactions of typing sera of the higher types, one of our recently recovered patients had a pneumococcus in his cerebrospinal fluid which showed the "quellung" reaction with both Type XI and Type XVI sera, it was later identified* as a pneumococcus beyond Type XXXIII Another patient had pneumococci in the spinal fluid which reacted with both Type VII and Type XXIV diagnostic sera, a characteristic of the so-called Type VII C pneumococcus Reveno and McLaughlin¹⁰ report one instance of bile-soluble encapsulated gram-positive diplococci which were agglutinated by both Type I and Type II sera, in all probability this phenomenon may have been accounted for by bivalent agglutinating sera Recently, Eriksson and Sjöberg¹¹ have recorded a case of meningitis secondary to a head injury which was caused by Type II and Type XX pneumococci, the genuineness of the multiple infection is substantiated by the fact that the patient improved after Type II serotherapy and the homologous organisms disappeared from the cerebrospinal fluid whereas the Type XX organisms remained, and cure was not effected until Type XX antiserum was employed Gaffney¹⁴ reported a case of meningitis in an infant in which *H. influenzae*, Type VIII pneumococcus or both were grown from the cerebrospinal fluid on all occasions, unfortunately, cultures were not obtained at necropsy when the exudate showed only gram negative bacilli Pray³³ has reported a case of osteomyelitis complicated by meningitis in which both a Type V pneumococcus and *Staphylococcus aureus* were isolated from both the blood and the spinal fluid

The association of pneumococcus with the tubercle bacillus in the cerebrospinal fluid was recorded by Achard and Horowitz¹⁵, biological identification was not recorded Two reports in the French literature^{12,13} attempted to show the association of meningococcus with pneumococcus in the causation of meningitis Identification of the organisms in both reports was made on the basis of tinctorial and morphological characters alone

PREDISPOSING FACTORS

Pneumococcal meningitis may attack at any age (table 2) It has been reported in the newborn^{16,17} The other extreme was exemplified by a patient, in our own series, who was more than 90 years of age In our own experience the age incidence curve has resembled somewhat that seen in pneumococcal pneumonia in this community with a peak in the first decade and another in the fifth decade A composite age incidence graph embracing all of the reported cases in the past 15 years shows more than half of the cases to occur before the age of 21, another peak does, however, occur in the fifth and sixth decades

*Through the courtesy of Miss Frances Clapp of the Lederle Laboratories, Pearl River New York

The influence of sex on the incidence of bacterial diseases in general is not well understood. In our own series, the male:female ratio of 2:1 prevails in pneumococcal infections of the meninges as well as of the lungs. A similar predominance of the infection among males is apparent in the reported cases.

There are recorded instances of pneumococcal meningitis among human beings of all colors and races, and there is very little evidence to show that any race shows any particular immunity or susceptibility. However, Ragiot,

TABLE II

	Died			Lived			Grand Total
	1927-36	1937-41	Total	1927-36	1937-41	Total	
Under 1 yr	21	33	54	7	12	16	73
1-10	12	58	70	20	65	85	155
11-20	9	29	38	10	60	63	108
21-30	11	26	35	12	25	36	74
31-40	9	29	38	4	28	30	70
41-50	10	39	48	2	26	28	77
51-60	7	27	34	2	7	9	43
61-70	4	16	19	0	2	1	22
71-80	1	4	5	0	1	1	6
81-90	1	0	1	0	0	0	1
Male	54	154	204	32	135	161	375
Female	25	86	111	26	81	99	218
White	62	115	176	48	158	200	383
Colored	9	17	25	4	22	26	52
January	9	15	24	8	15	23	47
February	7	12	19	5	24	27	48
March	8	16	24	7	17	20	48
April	1	14	15	5	18	23	38
May	5	5	9	2	24	25	36
June	3	7	10	5	10	13	25
July	2	4	6	1	7	7	14
August	3	2	5	4	14	15	23
September	2	2	4	0	7	7	11
October	6	10	16	3	11	14	30
November	4	4	8	3	10	12	21
December	3	10	13	2	11	13	26

Delbove and Nguyen-van-Huong¹⁸ do express the belief that the Annamites of Cochin-China are particularly good subjects for pneumococcal meningitis. The series at the Cincinnati General Hospital shows about the same ratio between white and negro patients as is seen in pneumococcal pneumonia.

The monthly incidence of the disease is shown in table 2. In a disease so closely related to diseases of the respiratory tract, such a distribution is not remarkable. The even distribution over the warmer months shows the effect of other factors than pneumococcal pneumonia in this disease.

The contagiousness of pneumococcal meningitis depends on the conditions favoring the dissemination of pneumococci. The disease occurred simultaneously in a man and his wife in the series at the Cincinnati General Hospital, but both patients had lobar pneumonia, in addition. Boyd, Baton

and Schlachman¹⁹ report the occurrences of primary Type II pneumococcus meningitis in a woman and her son, occurring one week apart

Pneumococcal meningitis is frequently classified as either primary or secondary. Since the cranial contents are normally not exposed to a pneumococcus-containing environment, the concept of primary meningitis is difficult to sustain. Surprisingly small collections of pneumococcal infectious processes are capable of invading the meninges either by direct extension or by metastasis. It is not unlikely that "cryptogenic" describes the evolution of the process more accurately. In our own experience we have not seen a case of pneumococcal meningitis which came to necropsy which did not show at least one focus containing the homologous type of pneumococcus elsewhere in the body. In the series of collected cases comprising this report less than 25 per cent were reported as being primary in origin. In-

TABLE III

	Died			Lived			Grand Total
	1927-36	1937-41	Total	1927-36	1937-41	Total	
Blood culture							
Positive	20	58	74	1	31	31	110
Negative	6	27	33	5	60	57	98
Focus							
Head injury	4	1	5	3	8	11	16
Skull fracture	7	15	22	2	14	16	38
Otitis media	19	83	102	18	82	96	202
Pneumonia	10	26	36	7	8	14	51
Sinuses	2	12	14	1	14	15	29
Upper respiratory infection	0	10	10	2	17	19	29
Endocarditis	8	15	19	0	0	0	23
Eye	2	1	3	0	1	1	4
Primary	20	31	51	18	47	59	116

fections within, or injuries to, the head were responsible for more than half of this series of meningitis. Frequently trivial trauma to the skull may be the only possible explanation for the onset of the meningitis^{20, 21}. Similarly, a long period may elapse between skull fracture and the onset of meningitis^{22, 23, 24}, and not infrequently, skull fracture may not be apparent even when suspected²⁵.

Otitis media and mastoiditis are listed as the cause of 202 out of 508 cases (table 3). Paranasal sinus disease, head injury and skull fracture accounted for 83 additional cases. Pneumonia accounted for 46 of our own cases, whereas it was recorded as the primary focus in only 51 of the collected cases. Pneumococcal endocarditis, rarely a primary disease, frequently terminates in meningitis⁹. The disease followed influenza and upper respiratory infections in only 5 per cent of the collected cases. Injuries to, or operations upon the eye very infrequently are followed by pneumococcal meningitis^{26, 27}. Unusual cases following cellulitis of the ear

pituitary tumor, lung abscess and pneumococcal peritonitis have been reported^{28, 7, 29, 30} Interestingly enough, lumbar puncture either as a diagnostic or a therapeutic measure was incriminated only twice as the predisposing cause of the meningitis^{31, 32} This confirms Pray's opinion that lumbar puncture was not a factor in causing the disease³³

The influence of previous infection or disease of the meninges is difficult to determine Recurrent infections are not uncommon Clark³⁴ reports a case in which the patient, an adult, recovered from an attack of pneumococcal meningitis but died two years later during a recurrence, the pneumococcus was not typed during the first attack, whereas a Type IV pneumococcus was responsible for the patient's death One of our patients recovered from three attacks of pneumococcal meningitis within nine months The organisms were of a different type in each instance being Types XVII, beyond XXXIII, and XXV respectively Recently Craddock and Bowers³⁵ reported a patient who had four attacks of meningitis within a year, with recovery in each instance Type XVII and Type XXVIII pneumococci were isolated during the first and third attacks respectively, whereas the spinal fluid cultures were sterile during the second and fourth Three instances^{36, 37, 38} of pneumococcal meningitis at varying intervals after recovery from hemolytic streptococcal meningitis appear in the literature, all recovered And the French literature³⁹ records a case in which an adult recovered from two attacks of meningococcal meningitis, as well as from a pneumococcal infection of the meninges

TREATMENT

The diversity of methods of therapy of pneumococcal meningitis, at least prior to 1937, is an indication of their inadequacy Continuous subarachnoid drainage with intravenous hypotonic saline, cisterno-lumbar lavage, optochin and its derivatives, intravenous iodine and charcoal and specific serotherapy have all had their advocates, but no worker employing any single method has been able to report an impressive series of cures

Table 4 represents a tabulation of the reported cases of pneumococcal meningitis in the available medical literature since 1926, exclusive of the cases listed in table 1 It is readily apparent that since 1936 there has been an increased interest in this disease, and many more cures are being effected There is no evidence that the incidence of the disease is increasing, on the contrary, many epidemiological reports of pneumonia and otitis media claim a decreased incidence of complications since the advent of chemotherapy for these diseases Both the augmented interest and the improved methods of treatment have undoubtedly been occasioned by the introduction of sulfanilamide and its derivatives In table 5 are tabulated by types the reported recoveries since 1926, to which have been added five recoveries not previously reported from the Cincinnati General Hospital Patients recovering from meningitis but dying shortly thereafter of other diseases

are not included Scott⁴⁰ and Toomey and Roach⁴¹ have reported recoveries from meningitis followed within a few weeks by death from pneumococcal endocarditis due to the homologous organism, one patient in our own series recovered from Type XIV pneumococcal meningitis, but died three weeks later of pneumococcal endocarditis

TABLE IV

Type	Died		Lived		Grand Total
	1927-36	1937-41	1927-36	1937-41	
I	5	25	4	21	55
II	6	2	2	6	16
III	18	53	8	42	121
IV	2	12		10	24
V		4		10	14
VI		11		8	19
VII		8		7	15
VIII		5		4	9
IX		2		1	3
X		6		3	9
XI		1		1	2
XII	2	1		1	4
XIII		1		6	7
XIV		7		3	10
XV		0		2	2
XVI		1		0	1
XVII		0		2	2
XVIII		12		10	22
XIX		4		7	11
XX		0		4	4
XXI		2		1	3
XXII	1	2		0	3
XXIII		3		4	7
XXIV		1		0	1
XXV		1		3	4
XXVII		1		1	2
XXVIII		1		4	5
XXIX		2		3	5
XXXI		2		3	5
XXXII				1	1
Above Group		5		2	7
Untyped	13	6	4	6	29
	39	74	44	58	215
Total	86	255	62	234	637

A review of this table shows that a sulfonamide was used alone in 102 of the cases, whereas a sulfonamide and some other drug, or operation were employed in 25 additional cases. Serum was the only therapeutic agent of import in 24 cases, and serum and sulfonamide therapy were combined in 70 cases. In five cases serum, sulfonamide and some other drug were administered. Thus, in more than 85 per cent of the recovered cases one of the sulfonamides or serum or both were employed as the significant therapeutic agents. Twelve of the patients recovered without any therapy which might conceivably be called specific, and five others recovered after surgical drainage of the primary focus.

TABLE V

Reference No	Blood Culture	Age	Focus	Treatment
Type I				
10	—	20	Head injury	Bivalent serum
71	—	28	Skull fracture	Serum
72	—	1	Upper respiratory infection	Daily lumbar puncture
73	Neg	57	Otitis media	Serum
74	—	16	Primary	Prontosil
75	—	26	Primary	Prontosil
36	—	17	Otitis media	Sulfapyridine
76	—	7	Primary	Sulfapyridine
77	—	11	Primary	Sulfanilamide
49	Pos	8	Otitis media	Sulfanilamide, sulfapyridine and serum
51	Neg	7	Otitis media	Sulfapyridine
7	Pos	15	Primary	Sulfanilamide and serum
43	Neg	44	Otitis media	Sulfapyridine, serum and mastoidectomy
65	—	<1	Pneumonia	Sulfapyridine and serum
78	—	47	? Sinus	Sulfanilamide and sulfapyridine
79	—	—	Primary	Sulfanilamide, sulfapyridine and serum
80	—	24	Otitis media	Prontosil album and soluseptazine
6	—	<1	Primary	None
61	—	23	Otitis media	Sulfanilamide and mastoidectomy
81	—	12	Otitis media	Serum and mastoidectomy
229	Pos	46	Otitis media	Sulfapyridine and serum
239	Neg	13	Otitis media	Sulfapyridine and serum
240	—	14	Otitis media	Sulfapyridine and serum
241	Neg	35	Primary	Sulfapyridine
241	Neg	25	Primary	Sulfapyridine
Type II				
82	—	31	Primary	Convalescent serum
83	—	<1	Pneumonia	Serum
19	—	43	Primary	Serum
19	—	14	Primary	Serum, Prontosil, and hydroxyethylapocupreime
84	Neg	5	Otitis media	Mastoidectomy and hyperthermia
11	—	24	Head injury	Sulfapyridine and specific sera (II and XX)
230	—	1	Upper respiratory infection	Sulfathiazole
241	Neg	19	Primary	Sulfapyridine
Type III				
85	Neg	7	Otitis media	Antimeningococcus serum
86	—	16	Otitis media	Serum and radical mastoidectomy
87	—	10	Otitis media	Mastoidectomy
88	—	30	Primary	KMnO ₄ , enemata
89	—	35	Otitis media	Forced drainage and radical mastoidectomy
90	Neg	50	Eye	Sulfathiazole and serum
31	—	32	? Spinal anesthesia	Antimeningococcus serum
91	—	35	Otitis media	Sulfapyridine, serum and mastoidectomy
92	—	40	Otitis media	Sulfapyridine, and petromastoidectomy
93	—	32	Otitis media	Labyrinthectomy
94	Neg	15	Otitis media	Mastoidectomy
64	—	5	—	Sulfanilamide and mastoidectomy
95	Neg	<1	Otitis media	Sulfapyridine
96	—	11	Otitis media	Sulfapyridine and serum

TABLE V (Continued)

Reference No	Blood Culture	Age	Focus	Treatment
Type III (Continued)				
49	—	39	Otitis media	Sulfapyridine, serum and mastoidectomy
50	—	36	Otitis media	Sulfapyridine
97	Neg	11	Otitis media	Sulfanilamide, mastoidectomy and hydroxyethylapocuprene
97	Neg	8	Otitis media	Sulfanilamide, mastoidectomy and hydroxyethylapocuprene
51	Neg	45	Otitis media	Sulfapyridine
51	Pos	11	Otitis media	Sulfapyridine
37	Pos	6	Otitis media	Sulfathiazole and serum
43	Neg	48	Otitis media	Sulfapyridine, serum and petrosectomy
98	—	39	Otitis media	Prontosil, serum and radical mastoidectomy
52	—	9	Otitis media	Sulfanilamide
99	—	48	Otitis media	Sulfapyridine
100	—	30	Primary	Sulfapyridine
54	—	15	Otitis media	Sulfapyridine, serum and apicectomy
101	—	18	Otitis media	Sulfapyridine
42	Neg	10	Otitis media	Sulfanilamide and mastoidectomy
102	Neg	25	Upper respiratory infection	Sulfapyridine
103	—	42	Sinus	Prontosil and operation
104	—	17	Otitis media	Sulfanilamide and mastoidectomy
105	—	54	Otitis media	Sulfanilamide
106	—	60	Otitis media	Sulfanilamide
107	—	40	Otitis media	Sulfanilamide
108	—	3	Sinus	Sulfanilamide and drainage of sinuses
109	—	17	Mastoid	Serum and mastoidectomy
110	—	35	Mastoid	Sulfapyridine, serum and mastoidectomy
44	Pos	46	Conjunctivitis	Sulfapyridine, serum and sulfadiazine
111	—	6	Otitis media	Sulfapyridine
111	—	7	Otitis media	Sulfapyridine
111	—	6	Otitis media	Sulfapyridine
112	Pos	22	Otitis media	Sulfapyridine and serum
112	Neg	12	Otitis media	Sulfapyridine and serum
113	Neg	46	Mastoid	Sulfathiazole and sulfamethylthiazole
231	Neg	7		Sulfathiazole
241	Neg	18	Primary	Sulfapyridine
Type IV				
114	—	7	Upper respiratory infection	Sulfapyridine
43	Pos	1	Otitis media	Sulfapyridine, serum and drainage of brain abscesses
43	—	8	Primary	Sulfapyridine and serum
115	Pos	—	Nose fracture	Continuous subarachnoid drainage
116	—	9	Sinus	Sulfapyridine, and radical frontal operation
32	Neg	5	Otitis media	Sulfanilamide and serum
117	Neg	40	Primary	Daily lumbar punctures
118	Neg	19	Primary	Sulfanilamide and serum
108	Pos	1	Primary	Sulfapyridine and serum
119	Pos	6	Otitis media	Sulfapyridine and serum
231	Neg	5		Sodium sulfapyridine and serum
239	Neg	62	Otitis media	Sulfanilamide and serum
Type V				
97	Neg	9	Otitis media	Sulfanilamide, mastoidectomy, and hydroxyethylapocuprene

TABLE V (Continued)

Reference No	Blood Culture	Age	Focus	Treatment
Type V (Continued)				
51	Neg	11	Otitis media	Sulfapyridine and mastoidectomy
43	Pos	13	Upper respiratory infection	Sulfapyridine, serum and mastoidectomy
120	Neg	9	Otitis media	Prontosil and mastoidectomy
121	—	10	Otitis media	Sulfapyridine and serum
41	Neg	12	Otitis media	Sulfapyridine and serum
41	Neg	15	Upper respiratory infection	Sulfanilamide and sulfapyridine
41	Neg	29	Otitis media	Sulfanilamide and sulfapyridine
122	Neg	6	Otitis media	Sulfapyridine, serum and operation
Type VI				
123	Neg	2	Otitis media	Sulfanilamide and serum
25	—	6	Nose fracture	Sulfapyridine and serum
7	Pos	8	Pneumonia	Sulfanilamide and serum
32	Neg	16	Sinus	Sulfanilamide and serum
124	Pos	<1	Primary	Sulfapyridine and serum
232	Pos	54	Nasal polyp	Sulfapyridine and serum
233	—	42	Skull fracture	Sulfathiazole and sulfapyridine
234	Pos	5	Skull fracture	Sulfapyridine
Type VII				
125	—	20	Sinus	Sulfanilamide, serum and radical frontal operation
59	Pos	33	Pneumonia	Sulfanilamide and serum
42	Neg	8	Skull fracture	Sulfanilamide and serum
61	—	48	Pneumonia	Sulfanilamide, serum and continuous drainage
126	—	19	Otitis media	Sulfapyridine, rubiazol, soluseptazine, and mastoidectomy
241	Neg	17	Primary	Sulfapyridine
231	Neg	12		Sodium sulfapyridine
Type VIII				
119	Pos	<1	Primary	Sulfapyridine and serum
112	—	13	Primary	Sulfanilamide and sulfapyridine
234	Pos	—		Sulfadiazine and serum
243	Neg	36	Pneumonia	Sulfadiazine
Type IX				
51	Neg	32	Upper respiratory infection	Sulfapyridine
Type X				
7	Pos	42	Primary	Sulfapyridine and serum
127	—	7	Primary	Sulfapyridine
229	—	19	Otitis media	Sulfapyridine
Type XI				
128	—	41	Otitis media Upper respiratory	Sulfanilamide, sulfapyridine and serum

TABLE V (Continued)

Reference No	Blood Culture	Age	Focus	Treatment
Type XII				
51	Pos	35	Primary	Sulfapyridine
Type XIII				
21	—	27	Mastoid	Sulfanilamide, serum and soluseptazine
32	Neg	15	Otitis media	Sulfanilamide and serum
41	Pos	31	Pneumonia	Sulfapyridine and serum
129	Neg	35	Mastoid	Sulfanilamide, azosulfamide and radical mastoid
231	Neg	6		Sodium sulfapyridine
235	—	40	Head injury	Sulfapyridine (1 relapse)
Type XIV				
130	Neg	16	Skull fracture	Sulfanilamide
131	—	1	Primary	Sulfanilamide, sulfapyridine and serum
132	—	10	Upper respiratory infection	Sulfapyridine and serum
Type XV				
133	Neg	22	Sinus	Sulfanilamide and daily lumbar punctures
43	—	14	Skull fracture	Sulfapyridine
Type XVII				
7	Pos	15	Otitis media	Sulfanilamide and serum
119	Neg	10	Otitis media	Sulfapyridine and serum
35	—	32	Primary	Sulfapyridine
Type XVIII				
35	Pos	14	Primary	Sulfapyridine and serum
43	Neg	8	Otitis media	Sulfanilamide, sulfapyridine, azosulfamide, and mastoidectomy
38	—	19	Otitis media	Sulfapyridine and serum
134	Neg	5	Primary	Sulfapyridine and serum
79	—	30	Primary	Sulfanilamide and sulfapyridine
42	Neg	19	Brain tumor	Sulfanilamide
108	—	—	Sinus	Sulfapyridine and serum
33	Pos	6	Otitis media	Sulfanilamide and serum
231	Neg	11		Sodium sulfapyridine and serum
231	Neg	3		Sodium sulfapyridine and serum
Type XIX				
63	—	7	Primary	Sulfanilamide, sulfapyridine and serum
137	Neg	23	Primary	Sulfapyridine
43	Pos	45	Otitis media	Sulfapyridine and serum
42	Neg	7	Skull fracture	Sulfanilamide and serum
135	Pos	11	Otitis media	Sulfapyridine, serum and mastoidectomy
136	—	2	Otitis media	Sulfapyridine and mastoidectomy
137	—	60	Otitis media	Sulfapyridine and serum

TABLE V (Continued)

Reference No	Blood Culture	Age	Focus	Treatment
Type XX				
138	Neg	18	Sinus	Radical frontal operation
139	Neg	14	Primary	Sulfapyridine and serum
55	—	41	Upper respiratory infection	Sulfapyridine
140	—	42	Otitis media	Sulfapyridine, serum and sulfanilamide
Type XXI				
141	Pos	9	Primary	Sulfapyridine and serum
Type XXIII				
49	Pos	53	Skull fracture	Sulfapyridine and serum
40	Neg	14	Primary	Sulfapyridine
51	Pos	49	Primary	Sulfapyridine
7	Neg	12	Skull fracture	Sulfapyridine and serum
Type XXV				
142	Pos	49	Upper respiratory infection	Sulfapyridine
51	Pos	34	Pneumonia	Sulfanilamide and sulfapyridine
119	Neg	11	Primary	Sulfathiazole
Type XXVII				
143	—	11	Primary	Sulfanilamide
Type XXVIII				
42	Neg	17	Head injury	Sulfanilamide
42	Neg	13	Primary	Sulfanilamide and serum
35	—	32	Primary	Sulfapyridine
144	Pos	49	Sinus	Sulfapyridine and serum
Type XXIX				
130	Neg	42	Brain operation	Sulfanilamide and dural repair
32	Neg	22	Nose operation	Sulfanilamide and serum
145	—	25	Pneumonia	Sulfapyridine and serum
Type XXXI				
7	Neg	76	Primary	Sulfanilamide and serum
32	Neg	50	Sinus	Sulfanilamide, serum and operation
232	—	—		Sulfonamide
Type XXXII				
112	Neg	12		Sulfapyridine and serum

TABLE V (Continued)

Reference No	Blood Culture	Age	Focus	Treatment
Types Above XXXII				
43	Neg	46	Primary	Sulfapyridine
119	Neg	10	Otitis media	Sulfathiazole and serum
236	—	10	Sinus	Sulfapyridine
Group IV				
146	Neg	11	Otitis media	Serum and Pregl's iodine
147	—	15	Otitis media	Vaccine and daily lumbar puncture
148	Neg	42	Sinus	Continuous drainage
149	—	5	Pneumonia	Serum
93	—	50	Dural repair	—
150	Neg	13	Otitis media	Sulfanilamide and mastoidectomy
151	—	38	Primary	Sulfapyridine
100	—	28	Upper respiratory infection	Sulfapyridine
152	Pos	6	Otitis media	Sulfapyridine
237	Neg	41	Osteoma of skull	Sulfapyridine
Untyped				
153	—	—	Mastoid	Mastoidectomy and urotropin
154	—	13	Primary	2% optochin
155	—	6	Primary	Serum
156	—	1	Otitis media	Serum and urotropin
157	—	1	Primary	None
158	—	8	Primary	Serum
159	—	5	Otitis media	5% mercurochrome
160	—	27	Primary	Bivalent serum
161	—	1	Pneumonia	Polyvalent serum, vaccine and "fixation" abscess
162	—	21	Otitis media	Serum, "fixation" abscess and mastoidectomy
163	—	1	—	Serum
164	—	25	Primary	Serum and optochin
165	—	5	Primary	Multiple punctures and antimeningococcus serum
166	—	43	Primary	Bivalent serum
167	—	—	Otitis media	Pn I serum, and daily lumbar punctures
168	Pos	36	—	Polyvalent serum and daily lumbar punctures
169	—	22	Otitis media	Urotropin and radical mastoidectomy
170	Neg	18	Primary	Serum and daily lumbar punctures
171	—	26	Primary	Mixed serum
172	—	5	Primary	Serum
34	—	29	Head injury	Daily lumbar punctures
173	—	25	Primary	Serum and mercurochrome
174	—	59	Primary	None
175	—	21	Skull fracture	Huntoon's antibody
176	—	3	Pneumonia	Daily drainage of subarachnoid fluid
177	—	16	Pneumonia	Felton's serum
178	—	1	—	None
179	—	13	Otitis media	Daily lumbar punctures
180	—	1	Primary	Serum
181	—	9	Otitis media	Serum
182	—	5	Primary	Serum
183	—	21	Pneumonia	Serum
183	—	10	Pneumonia	Serum
184	—	5	—	Optochin
185	—	—	Otitis media	Mastoidectomy
186	—	2	Head injury	None

TABLE V (Continued)

Reference No	Blood Culture	Age	Focus	Treatment
Untyped (Continued)				
187	—	6	Primary	Serum
188	—	14	Primary	Haptinogen
188	—	28	Primary	Haptinogen
188	—	19	Upper respiratory infection	Haptinogen
189	—	1	Primary	None
190	—	—	Primary	Hydroxyethylapocuprene
191	—	8	Otitis media	Mastoidectomy
192	—	9	Otitis media	Daily lumbar punctures
193	—	5	—	Sulfanilamide and serum
193	—	9	—	Sulfanilamide and serum
193	—	6	—	Sulfanilamide
194	—	4	Otitis media	Rubiazol, neococcyll, soluseptazine and serum
24	—	8	Skull fracture	Sulfapyridine, septoplax and dural repair
195	—	8	Otitis media	Sulfapyridine
196	—	1	Upper respiratory infection	Soluseptazine, sulfapyridine, and daily lumbar punctures
196	—	6	Otitis media	Sulfapyridine and soluseptazine
197	—	3	Otitis media	Sulfapyridine
198	—	3	Upper respiratory infection	Sulfapyridine
199	—	2	Otitis media	Serum and optochin
200	—	5	Primary	Polyvalent serum
47	—	5	Otitis media	Sulfanilamide and antimeningococcus serum
201	Neg	15	Otitis media	Benzyl sulfanilamide and mastoidectomy
76	—	42	Sinus	Sulfapyridine
202	—	4	Primary	Sulfapyridine and serum
203	—	53	Primary	Sulfapyridine and "1162F"
204	—	37	Primary	Sulfapyridine
39	—	26	Primary	Sulfapyridine
205	—	35	Sinus	Operation and intravenous charcoal
49	—	52	Skull fracture	Sulfapyridine
206	—	15	Otitis media	Sulfapyridine, soluseptazine and streptalbumin
207	—	17	Otitis media	Sulfapyridine and radical mastoidectomy
208	—	39	Primary	Sulfanilamide and electrargol
209	—	8	Primary	Prontosil
210	—	7	Upper respiratory infection	Sulfapyridine
211	—	14	Primary	Sulfapyridine, soluseptazine and bivalent serum
212	—	24	Upper respiratory infection	Sulfapyridine
53	—	34	Primary	Sulfapyridine
213	—	18	Influenza	Sulfapyridine
213	—	27	Primary	Sulfapyridine
214	—	39	Otitis media	Sulfapyridine, soluseptazine and mastoidectomy
215	—	6	—	Sulfapyridine
215	—	13	—	Sulfapyridine
216	—	1	Primary	Sulfanilamide and serum
217	Neg	19	Primary	Prontosil, and frequent lumbar punctures
218	—	11	—	Sulfapyridine and forced drainage
218	—	7	—	Sulfapyridine and forced drainage
219	—	27	Otitis media	Human serum
220	—	1	—	None
221	—	24	Primary	Sulfapyridine
222	—	30	Nose fracture	Soluseptazine
223	—	1	Otitis media	Septoplax
224	—	20	—	Serum and vaccine
62	—	24	Skull fracture	Elevation of bone, numerous lumbar punctures

TABLE V (Continued)

Reference No	Blood Culture	Age	Focus	Treatment
Untyped (Continued)				
225	—	2	Upper respiratory infection	Sulfanilamide
226	—	64	Pneumonia	Sulfapyridine and "1162F"
226	—	48	Primary	Sulfapyridine and "1162F"
227	—	39	Otitis media	Sulfapyridine
228	Neg	27	—	Sulfapyridine
126	—	32	Otitis media	Sulfapyridine and mastoidectomy
231	Neg	20	—	Sodium sulfapyridine
238	—	22	None	Sulfapyridine
242	Pos	19	Primary	Sulfapyridine
244	—	15	Otitis media	Sulfapyridine
245	—	<1	—	Sulfapyridine
245	—	<1	—	Sulfapyridine
245	—	<1	—	Sulfapyridine

The hope of discovery of some common denominator of these recoveries occasioned this review, yet the key to the cure of pneumococcal meningitis is not so apparent. It is certain that the sulfonamides either alone or in combination with specific serum seem to be curative in certain cases of pneumococcal meningitis. Finland, Brown, and Rauh,⁴² in 1938, were the first to advocate a combined régime of serum and sulfonamide therapy in this disease, and reported six consecutive cures employing this method of treatment. Similarly, Neal and her associates⁴³ and Rhoads et al.,⁷ who reported 10 and seven recoveries respectively, felt that combined therapy offered the greatest hope of success. The six patients who recovered at the Cincinnati General Hospital received serum as well as one of the sulfonamides. The choice of sulfonamide does not appear to be especially important, sulfapyridine has been employed most frequently because of its bacteriostatic superiority over sulfanilamide, and because its diffusion into the cerebrospinal fluid is greater than that of sulfathiazole. Recently sulfadiazine has been employed in curing several patients with pneumococcal meningitis^{14, 234, 243}. However, the poorer diffusibility of sulfathiazole is not a necessary contraindication to its use, for it has been shown to be a very effective agent in the treatment of meningococcal meningitis⁴⁵ as well as staphylococcal meningitis⁴⁶. In our own experience, three of the patients recovered after receiving the latter drug and the lower blood and cerebrospinal fluid concentration did not seem to be disadvantageous. Dosage should be determined by the conditions surrounding the individual case. The early administration of the chemical by the intravenous route, usually in the form of the sodium salt, is accepted and recommended by most workers because the lag due to absorption is thereby obviated, of course, in comatose patients this method is almost compulsory. Further time may be gained by an initial intrathecal injection of a solution of the drug, Neal and her as-

sociates¹¹ found a 2 per cent solution of sodium sulfapyridine feasible for this purpose and without untoward reaction. After attaining a desired level, further therapy can be continued by the intravenous or oral route. In general, therapy should not be discontinued for several days after the cerebrospinal fluid has been sterilized. Recrudescences in pneumococcal meningitis are notorious^{13, 17, 18, 19, 50, 51, 52, 53, 54, 55}, most frequently, inadequate treatment is the cause, but the possibility of undrained or unresolved purulent foci should always be kept in mind.

In a few well-authenticated cases, the organisms have apparently become resistant or "fast" during the course of treatment^{20, 56, 57, 58}. Further chemotherapy is usually useless then, and serum treatment should be employed without further delay.

Theoretically, a combination of serum therapy and chemotherapy is not unsound. There are still too few cases on record to determine whether such a combination of therapy is more effective than chemotherapy alone. Several workers have reported improvement of their patients under chemotherapy but without cure until serotherapy had been employed. At the present time, it seems the wiser plan to give the patient the benefit of both types of treatment.

The amount of serum cannot be stated dogmatically. Probably 100,000 units will suffice for most cases. If tests for serum adequacy are available and reliable, they could well be employed. Otherwise, the total amount of serum should depend on many factors, probably the most important being the age of the disease, the extent of pneumococcal disease elsewhere in the body, and the degree of bacteremia. Query⁵⁹ used 600,000 units in treating a case secondary to pneumonia and empyema, and Rhoads et al.⁷ employed an equal amount in curing a patient with primary meningitis. Finland, Brown and Rauh⁴² felt that the intrathecal injection of large amounts of concentrated serum might be harmful, but advised the subarachnoid administration of human serum containing specific antibody as well as complement. Neal et al.⁴³ also employed the subarachnoid route, as well as the intravenous, for serum administration. The importance of this factor is by no means clear. Our own recovered patients as well as many others reported in the literature did not receive serum by this route.

The elimination or drainage of accessible purulent foci in the treatment of pneumococcal infections is fundamental, and meningitis affords no exception. The literature abounds with cases exemplifying failure to heed this rule with the consequent reinfection and ultimate death of the patient. An undrained middle ear,⁶⁰ sinus or mastoid may frequently be asymptomatic, yet be the cause for the continuance of the infection. And in meningitis secondary to pneumonia, an empyema of the pleural cavity may be easily overlooked.

The frequency with which lumbar punctures should be performed has long been a moot point. At one time continuous drainage of the subarachnoid space was recommended in the treatment of pneumococcal as well as

other forms of bacterial meningitis. The cases collected in this report exemplify all variations in this respect. Slaughter and Sydenstricker⁶¹ cured two patients with continuous drainage of the subarachnoid space, Toone and Higginbotham's⁶² patient recovered after 92 subarachnoid taps in the course of 129 days, whereas Leichenger and Abelson⁶³ performed only one lumbar puncture. The trend seems definitely to be in the direction of fewer subarachnoid drainages. In our own experience lumbar punctures seem to be indicated for diagnosis and as guides to adequacy of treatment.

The effect of the sulfonamides as a prophylactic requires further observation. Theoretically, it seems to be sound and judicious to employ this drug locally after operations on the skull or following skull fractures. On the other hand, several workers report the onset of meningitis during the course of sulfonamide therapy for the primary infection^{25, 48, 64, 65, 66}. Kolmer and Amano⁶⁷ suggested the specific prophylaxis of pneumococcal meningitis by means of vaccine. Goldman and Hirschberger⁶⁸ applied the principle clinically, and thought it to be of value in reducing the intracranial complications of mastoiditis, the series was not well controlled. In view of the uncertainty of development of active immunity against the pneumococcus by vaccines, prophylaxis by this method can scarcely be recommended very seriously.

RESULTS OF TREATMENT

There is very little doubt that pneumococcal meningitis formerly was a very fatal disease. There is no record of a recovery at the Cincinnati General Hospital prior to 1937. In most communities the death rate has been considered to be in excess of 95 per cent.

Undoubtedly, the case mortality rate of pneumococcal meningitis has been lowered. It is hazardous to be more specific in evaluating a series of collected cases, for the case reports of recoveries are much more likely to be published than are the failures of therapy.

It appears, however, that this saving of lives affects all age groups, and especially those between one and 20. The prognosis in infancy remains grave. The improved method of treatment has no predilection for a certain type of pneumococcus, and there is no evidence that any certain type is especially resistant to this therapy. As a matter of fact, the percentile increase of cures of Type III pneumococcal meningitis is striking in view of the mortality of Type III pneumococcal pneumonia. Meningitis secondary to infections within the head or injuries to the head has been more amenable than that secondary to pneumonia, this might be expected because the primary focus is more likely to yield to direct treatment and because bacteremia is less likely to become a factor.

Neal, Applebaum and Jackson,⁴³ in an analysis of their own 30 cases, concluded that bacteremia had no particular bearing on the outcome of the disease. An analysis of this series of 637 cases compels the opposite con-

clusion Of the 296 recovered cases, only 31 had positive cultures, 57 had negative reports, and the remainder were either uncultured or not reported Of the 341 patients who died, 74 had bacteremia, 33 had negative blood cultures, and the remainder were not cultured Bacteremia is of paramount prognostic import in pneumococcal pneumonia,⁶⁰ and probably is a big factor in determining the outcome of pneumococcal disease of the meninges

Stewart, as well as Kolmer and more recent investigators, predicted the difficulties of treatment of this disease in their work on animals They noted the tendency of the pneumococcus to provoke the early outpouring of a massive fibrinous exudate The discovery of highly diffusible bacteriostatic drugs undoubtedly adds to the humoral defense of the body in that respect They also noted that recovery did not occur in experimentally-produced disease if there was more than a short interval between onset of the disease and institution of therapy Similarly, in the human disease earlier diagnosis is necessary if best results are to be obtained

Robertson⁷⁰ in England thinks that the case mortality rate of the disease might be 25 per cent or less at present, citing his recent experience as proof Such optimism seems unjustified from this review, in this country there is no reason to believe that such results are approximated by even a wide margin

SUMMARY

A review of the available literature since 1926 concerning pneumococcal meningitis is presented

It is essentially a disease of younger people but may occur at any age

It usually follows disease of the ear, mastoid and sinuses, pneumonia, or injuries to the skull, frequently, the disease appears to be primary in origin

Important factors in determining the prognosis are age of patient, duration of disease before treatment, presence or absence of bacteremia, and the extent and distribution of primary foci

Successful treatment depends, in the main, on prompt and vigorous sulfonamide therapy, intravenous injection of specific concentrated serum, and the drainage of accessible foci of pneumococcal pus

The disease continues to have a serious prognosis, and demands early recognition if recovery is to occur

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PRIMARY AMYLOIDOSIS; A REPORT OF THREE CASES^{*}

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PRIMARY or idiopathic amyloidosis is a rare and poorly understood disease, although it was recognized as far back as 1856, when it was described by Wilks¹. In the Guy's Hospital Report of that year, Wilks brought attention to this pathologic entity, which he named "lardaceous disease". Since his time, the number of reported autopsy-proved cases has been small. It is the purpose of this paper to add three cases to the literature and to make certain clinical observations concerning them.

Recently several American authors have published case reports of primary amyloidosis. In 1936 Kerwin² reported two cases, and in 1939 Koletsky and Stecher³ reported one case and noted some 30 other cases in the literature. After that report, Binford⁴ had one patient with proved primary amyloidosis, and more recently, Pearson, Rice, and Dickens⁵ published two cases which they believed to be the first which had occurred in negroes. In 1930, however, Larsen⁶ had noticed the occurrence of primary myocardial amyloidosis in a negro man 65 years of age.

In 120,785 admissions to the Medical and Surgical services of the Peter Bent Brigham Hospital during the period from April 12, 1913, to June 1, 1941, there were 35 cases diagnosed as amyloid disease. This diagnosis was proved in 23 out of 4,551 autopsies performed during this time. In 20 of these, amyloidosis was secondary to such chronic diseases as tuberculosis, syphilis, lung abscess, pyelonephritis, and various other forms of chronic suppuration. In only three cases was amyloidosis present without other major pathologic findings, and therefore, primary. The distinction between primary and secondary amyloidosis is well recognized and has been well defined by Reimann and others⁷ and by Lubarsch⁸.

CASE REPORTS

Case 1 D. B., a 61-year-old Italian scissors-grinder, entered the hospital February 21, 1941, and was discharged March 2, 1941. His chief complaint was substernal pain and dyspnea of 6 months' duration. His family history was irrelevant. He had a past history of generalized rheumatism and fever of three days' duration at the age of 40, and a mild dry cough for years.

The present illness began six months before entry, with attacks of squeezing and gripping substernal pain with dyspnea. The pain radiated to the right upper quadrant and shoulder, and was definitely and exclusively related to exertion and relieved by rest. The attacks increased in frequency from two to four daily at the onset, to 12 to 14 on admission, and were severe enough to prevent his working during the two

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months prior to admission. He had progressively increasing edema of the lower extremities for one month before entering the hospital. Four months before admission, he awakened one morning to find both eyes black and blue, an egg-sized mass in the left axilla, and a purplish symptomless rash over the left arm and pectoral region. He had lost 20 pounds in six months. During the week before admission he had two spells of paroxysmal nocturnal dyspnea.

Physical Examination The patient was a moderately obese Italian male in no apparent distress. The vital signs were normal, and his blood pressure was 120 mm Hg systolic and 80 mm diastolic. There were large purpuric areas over the left upper arm, axilla, and left half of the thorax. His eyes, including the fundi, were normal. He had marked dental caries and pyorrhea. In the left axilla there was a firm, non-tender, partially fixed, lemon-sized mass with several neighboring, smaller, similar, discrete nodes. In the right axilla there were similar walnut-sized nodes. The inguinal nodes were only slightly enlarged. The heart seemed moderately enlarged to the left, the sounds were clear, regular, without murmurs. There were signs of fluid at the right lung base and many coarse râles at both bases. The abdomen was soft with no detectable ascites. A smooth, firm, tender liver edge was felt down a hand's breadth in the right upper quadrant, and a smooth, firm, non-tender spleen extended down a similar distance on the left. There was a 3+ soft edema of the sacrum, scrotum, and lower extremities. No venous distention was observed.

Laboratory Data The blood Hinton and Wassermann reactions were negative. The urine on three examinations concentrated to 1014. There was a small amount of protein once, and sediments were negative. Blood counts, smear, hemoglobin and hematocrit determinations were normal. The platelets numbered 136,000 per cubic millimeter. The clotting and bleeding times were normal, and the tourniquet test was within normal limits. Stools were negative for blood. The sputum was thick, green, and purulent, it was negative for tubercle bacilli. The serum non-protein nitrogen was 37 mg per 100 c.c., the icteric index was 5, and the total serum protein 61 grams per 100 c.c. The venous pressure was 110 mm of water, the normal being 150 mm. Decholin circulation time was 33 seconds. An electrocardiogram showed mild left axis deviation, low electromotive force, and a P-R interval of 0.24 second with Lead IV normal. Roentgenologic examination showed the heart, especially the left ventricle, to be markedly enlarged, and the aorta tortuous. There was an irregular patch of consolidation at the right base and some fluid in the right costophrenic angle. A film of the abdomen was non-contributory.

Hospital Course The vital signs remained normal throughout the patient's hospital course. Four days after admission biopsy of the left axillary mass was undertaken, and it was found to consist almost entirely of necrotic blood clot. One of the inguinal nodes was removed instead (figure 1). The next day there was considerable bleeding from the axillary wound, and the hemoglobin fell to 64 per cent (photoelectric method). Prothrombin time was found to be 37 seconds (normal control 23 seconds). The bleeding was controlled by pressure bandages, and 400 c.c. of whole blood were given cautiously. On the sixth day digitalis was begun, and by the ninth day he had received 13 grams orally. On the afternoon of the ninth day he complained of weakness and dyspnea, and his pulse became slow and irregular. The electrocardiogram now showed a slow, slightly irregular rhythm due to variation of the auricular pacemaker, but there were no other changes. That night he complained of severe, intermittent, epigastric pain. He vomited 200 c.c. of dark fluid material, which was guaiac positive. He became increasingly dyspneic and restless. His blood pressure fell to 70 mm Hg systolic and 40 mm diastolic, but the peripheral circulation remained good and the pulse did not rise over 72. He died in his sleep a few hours later.

Biopsy Diagnosis Nodes from the axilla and groins showed a large amount of dense, homogenous material in walls of blood vessels and lymphatics and beneath the lining of the sinuses, consistent with amyloidosis of the lymph nodes (figure 1).

Clinical Diagnoses Myocardial infarction due to arteriosclerotic coronary thrombosis, malignant lymphoma, possible Hodgkin's disease, possible gastrointestinal hemorrhage

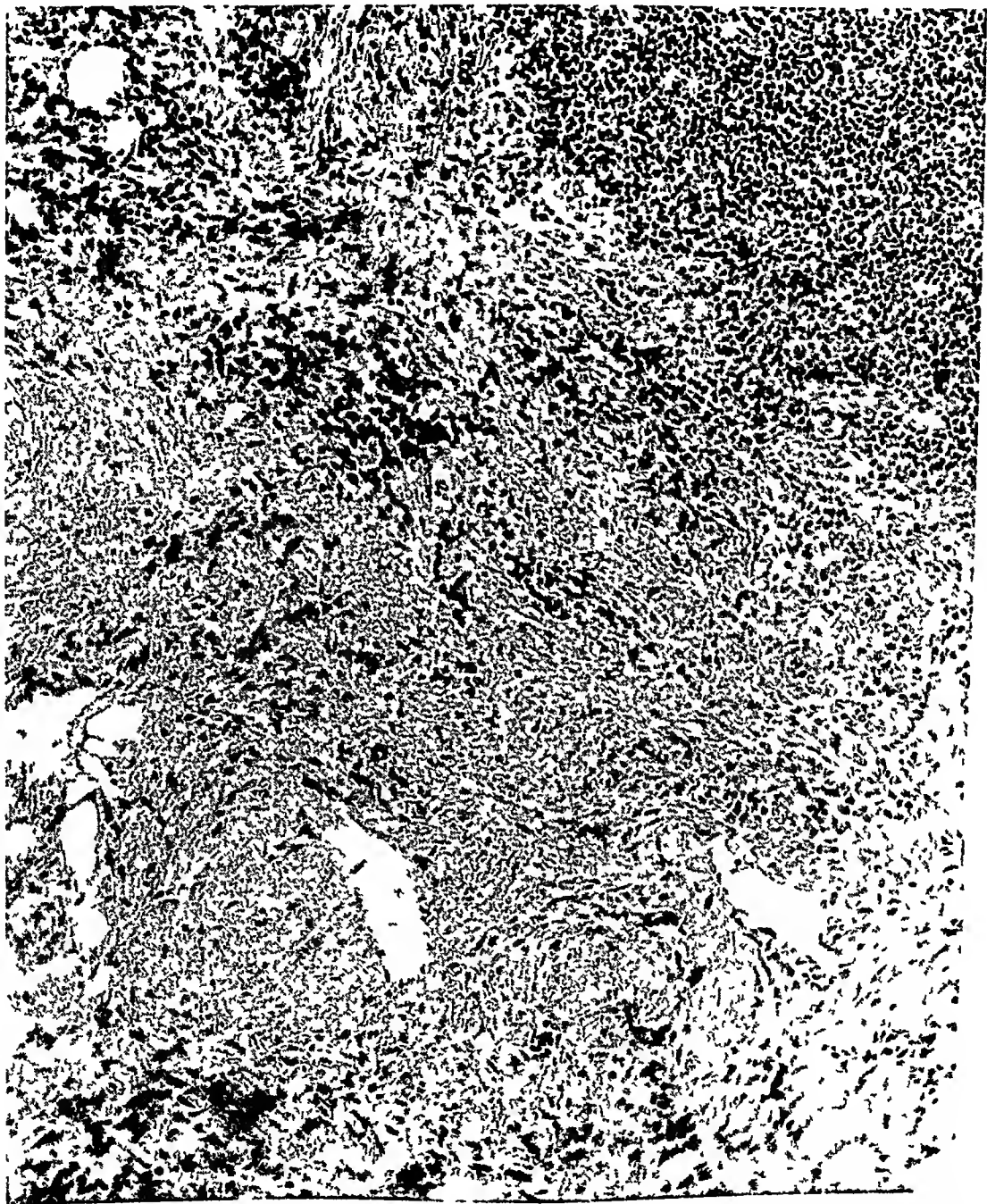


FIG 1 *Case 1* Biopsy of a lymph node ($\times 150$) There is a large amount of dense homogenous material in the walls of the blood vessels and lymphatics and beneath the lining of the sinuses This material is amyloid

Postmortem Diagnoses Generalized amyloidosis, cardiac hypertrophy and dilatation, purpura, chronic passive congestion of the viscera, focal hemorrhage and necrosis of the liver, dependent edema, hydropericardium, hydrothorax, pulmonary emphysema and atelectasis, pleural adhesions, diverticula of the colon, peritoneal adhesions, and left hydrocele.

The liver, spleen, kidneys, and blood vessels in every location except in the spinal cord showed deposition of amyloid material. The heart weighed 670 grams and was well dilated. The coronary arteries were tortuous and the lumina narrowed but otherwise showed no gross changes. Microscopic examination, however, showed that in the coronary vessels there were abundant subintimal deposits of hyaline material which had the characteristic staining properties of amyloid. This was also the case with material found within the epicardium, endocardium, and myocardium, as well as within the leaflet of the tricuspid valve (figure 2)

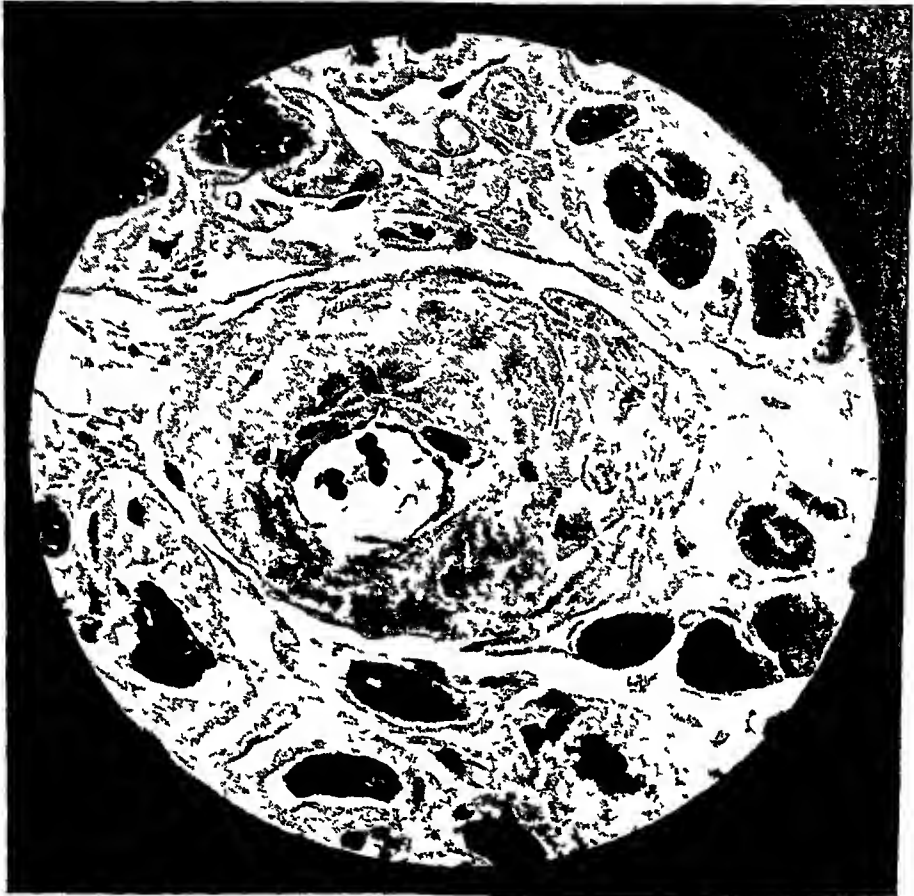


FIG 2 *Case 1* A section of myocardium ($\times 520$) A small blood vessel is seen in cross-section. There is heavy sub-intimal deposition of amyloid. This material can also be seen within and around the nearby muscle fibers.

Because of the multiplicity of causes and symptoms, it is difficult to evaluate cardiac failure as the direct cause of death in such a widespread systemic disease as primary amyloidosis. However, the fact that this disease can kill by direct involvement of the heart is known. Kerwin in 1936² described two cases of death due to primary amyloid disease of the heart, and one of his cases closely resembled the above. He also mentioned two reported cases, which seemed to be primary amyloidosis with deaths caused by cardiac disease^{9, 10}. Perla and Gross¹¹ reported another case, a 54-year-old

woman who had chest pain, dyspnea, low blood pressure, and signs of cardiac failure, with sudden death. At autopsy it was found that she had primary amyloid disease of the heart and of other organs. Budd¹² reported a case of amyloid disease of the heart which he called primary, but in which there were no cardiac symptoms. His patient also had carcinoma of the bladder and chronic suppuration of the urinary tract, which cast considerable doubt on the primary or idiopathic aspect of this case.

In Binford's report⁴ the patient had cardiac asthma and eventual heart failure, with electrocardiographic evidence of old myocardial infarction. At postmortem examination, it was found that there was stenosing amyloidosis of the coronary vessels and interstitial deposition of hyaline substance in the myocardium, with no associated chronic disease. One of the two cases reported by Pearson⁵ was cardiac, but was complicated by the presence of a previously existing hypertension and cardiac failure. Therefore, it cannot be included in this category.

As indicated by our case, primary amyloidosis of the heart may greatly resemble the syndrome of sclerotic coronary artery disease with signs and symptoms of coronary failure and myocardial insufficiency. It holds position with the other rare but real causes of heart disease, such as arteriovenous aneurysms, nutritional deficiencies, and others described by Weill.¹³ As he points out, the diagnosis in such cases is difficult but can be suspected.

The diagnosis can be made by the signs and symptoms typical of coronary artery disease and myocardial insufficiency in the absence of previously existing hypertension and in the presence of an enlarged liver, spleen, and lymph nodes. This can be confirmed by lymph node biopsy and by a positive Congo red test. It is interesting to note the presence of purpura in this case. Purpura has been previously described by others in primary amyloidosis⁵ and is presumably caused by vascular damage due to intercapillary penetration of the amyloid substance.

According to Reimann, Koucky, and Eklund,⁷ one of the features of primary amyloidosis is that it reacts weakly, if at all, with the usual differentiating stains. This was not true in this case. The kidneys, liver, spleen, and heart all took the iodine, methyl violet, and Congo red stains very well.

Case 2 C S, a 57-year-old white housewife, entered the hospital October 29, 1937, and was discharged November 19, 1937. Her chief complaints were constipation for two years, weight loss for one year, and fatigue for seven months. Her family history was irrelevant. She had had rheumatic fever at the age of 10, at which time she was told that her heart was affected. She had mild cystitis three years before admission. This cleared up immediately on treatment, and recurred one year later, when it cleared up permanently with renewal of treatment.

Present illness began 10 months before admission, when she first noted some weakness and weight loss. On routine examination, her physician found an enlarged liver and proteinuria. For the next six months she was kept on a high protein diet, and her tonsils and teeth were removed in the search for foci of infection. During the four months preceding admission, she was treated in the Out-Patient Department of the Peter Bent Brigham Hospital. Here it was noted that her liver was

enlarged, she was slowly losing weight and strength, her urine consistently showed a large trace of protein, with rare casts and white blood cells. On roentgenologic examination the gastrointestinal tract was found to be normal. Intravenous urograms showed a normal urinary tract. Because of these positive findings and the fact that she had lost 35 pounds since the onset of her illness, she was referred into the hospital for further study, with the tentative diagnoses of low grade nephrosis, hepatic enlargement of unknown cause, and possible neoplasm.

On physical examination, the patient appeared to be a well-developed, middle-aged, white woman showing signs of recent weight loss. The vital signs were normal, and the blood pressure was 110 mm Hg systolic and 76 mm diastolic. There were ecchymotic areas on the buccal mucous membranes. The lungs were clear to percussion and auscultation. The heart was normal in size, its rhythm was regular, and there was an apical presystolic murmur with accentuation of the first sound. The abdomen was soft. The liver, which was enlarged four fingers' breadth below the right costal margin, was smooth, hard, and tender. Although the spleen was not palpable, the inguinal glands were slightly enlarged. Neurologic, pelvic, and rectal examinations were negative. The ophthalmoscopic examination revealed slight retinal arteriosclerosis.

Laboratory Data The blood Hinton and Wassermann tests were negative. The urine was concentrated to 1015, and persistently showed a trace to a large trace of protein, rare, finely granular casts, an occasional white blood cell, and a rare red blood cell. Red cell counts and hemoglobin concentration were normal. The white cell count, which was normal on entry, increased to 33,000 with the terminal fever. The phthalein excretion was 52 per cent in two hours. Studies of the blood chemistry revealed a non-protein nitrogen of 27 mg per 100 cc, urea nitrogen of 13 mg per 100 cc. The total protein concentration was 5.5 gm per 100 cc, with an albumin fraction of 2.6 grams, and a globulin of 2.9 grams per 100 cc. Fasting gastric analysis revealed 53 units of free acid and 61 of combined acid. The Congo red test was positive, showing 100 per cent withdrawal of the dye from the blood stream in an hour's time. The blood sedimentation rate was 0.2 mm per minute. Examinations of the stools with guaiac were + to +++++, and terminally they contained bright red blood. Two blood cultures were negative.

Hospital Course The patient got steadily worse with increasing weakness and emaciation. She had a daily fever around 100° F until four days before death, when it began to rise steadily to 105° F. For three days before death she passed watery stools which were grossly bloody. Small pinhead-sized petechiae were found in the conjunctivae. Death occurred with hyperpyrexia and cardiac failure.

Clinical Diagnoses Chronic nephritis, amyloidosis, rheumatic heart disease, possible subacute bacterial endocarditis.

Postmortem Diagnoses Amyloidosis of the spleen, liver, heart, brain, parathyroid glands, stomach, colon, adrenal glands, and kidneys, bacterial endocarditis of the mitral valves (streptococcus), rheumatic mitral valvulitis, healed, polypoid submucosal hemorrhages of the colon with one area of ulceration, petechiae of the kidneys and small intestine and generalized streptococcus peritonitis, slight atheromatous change in the aorta, fibrosed ovaries.

The heart, which weighed 320 grams, seemed somewhat enlarged and hypertrophied when studied in situ. On dissection, the valves of the right side of the heart were thin, membranous, and freely movable. The mitral valve showed a definite thickening of its leaflets and a distinct nodularity along its free edge. Numerous, small, warty excrescences, which had the appearance of recent vegetations, were situated on the anterior cusps of the mitral valve and on its auricular surface. The aortic valve showed slight thickening, especially along the free edges. There was also a definite thickening of the annulus fibrosus. Microscopic examination of the

mitral valve revealed hyaline thickening of the valve, and polymorphonuclear leukocytes and small bits of fibrin adherent to its frayed surface

The relationship of primary amyloidosis to rheumatic heart disease and bacterial endocarditis is interesting. In this case the endocarditis was undoubtedly a terminal concomitant. The pathologist's description of the endocarditis was "There are numerous warty excrescences which have the appearance of recent vegetations." Clinically, the hepatomegaly and proteinuria were noted by her own doctor 10 months before admission. During the six months before admission, while she was being followed in the Out-Patient Department, her temperature was normal and she had none of the signs and symptoms of bacterial endocarditis. It was only a few days before death that petechiae were found, but the blood cultures failed to become positive for streptococci. This patient's initial rheumatic infection occurred 47 years before death.

Amyloid disease occurring secondary to rheumatic fever has been reported by Beattie¹⁴. He noted four cases in patients under 28 years of age, all having histories of acute rheumatic fever from seven months to several years before death. At postmortem examination two of his cases had bacterial endocarditis, superimposed on their rheumatic valvulitis. In our patient, however, there was no recent recognizable attack of acute rheumatic fever to which the amyloid disease might be secondary. Fishberg¹⁵ mentioned the fact that he has seen these two diseases occurring together, but he did not say whether the amyloidosis was primary or secondary to the bacterial endocarditis.

Case 3 W K, a 52-year-old plumber, was admitted for the last time on May 24, 1928, and was discharged May 25, 1928. He had had three previous admissions for the same disease. His chief complaints were pain and paralysis of the right leg. His family history was irrelevant. In addition to the usual childhood diseases he had had pneumonia at 25 and gonorrhea at 25 and again at 42.

His present illness began about August 1925, two years and nine months before his last entry, with swelling of the legs and scrotum, most marked at nightfall. He was studied at the Faulkner Hospital in Boston, in November 1925, at which time he was told he had albumin in his urine and should limit his diet and fluids. He did not improve and was admitted to the wards of the Peter Bent Brigham Hospital for the first time in November 1926. At that time he had a marked pallor, anasarca, and ascites. His blood pressure was 145 mm Hg systolic and 80 mm diastolic. The blood chemistry was normal. Phthalein excretion was 40 per cent in two hours, and his basal metabolic rate was -20 . The urine showed $+++$ and $++++$ albumin with numerous casts. He improved on a high protein diet, with calcium chloride as a diuretic. After discharge he was followed in the Out-Patient Department. His edema gradually reaccumulated. Laboratory data remained unchanged except for his blood pressure, which decreased to less than 120 mm Hg, and the metabolic rate, which responded with thyroid and rose to -4 .

His second admission was in October 1927, at which time he had edema of the hands, lower arms and body from the fifth rib down. An abdominal paracentesis yielded 6,200 cc of fluid. Laboratory findings were as before except for the phthalein excretion, which was 65 per cent in two hours. He became free of most of his edema, and was discharged to the Out-Patient Department. Again the edema

reaccumulated rapidly and he was admitted for the third time in December 1927. His edema and ascites were greater than on previous admissions, but responded to tapping and mercurial diuretics, so that on discharge he had lost 10.2 kilograms. The urine now showed albumin, red and white cells, and casts. The stools were benzidine positive. Once more he was followed in the Renal Clinic, and he was maintained on high protein diets and ammonium chloride and ammonium nitrate with salyrgan were administered. Abdominal taps were done when indicated, the last tap, five days before his final entry, yielding 12 quarts of fluid. The serum total protein during this period was 4.94 grams per 100 c.c., with albumin 2.44 grams and globulin 2.50 grams. On the morning of his last admission he awoke to find his right leg tender, more swollen than the left, and very painful and paralyzed.

On physical examination, the patient appeared to be a poorly developed, edematous, chronically ill male, complaining bitterly of pain in his right leg. His temperature was 99.8° F, the pulse was 110, and respirations were 26. His blood pressure was 85 mm Hg systolic and 55 mm diastolic. His eyes, ears, nose, throat, and lungs were normal. The heart was not enlarged, the sounds were regular and of fair quality, without murmurs. The abdomen was slightly distended, symmetrical, with shifting dullness in the flanks and edema of the lower abdominal wall. The arms were normal, but the legs both showed pitting edema, the right more so than the left. The right leg was also warmer, redder, and more tender than the left.

Laboratory Data The blood Wassermann reaction was negative. The urine concentrated to 1022 and showed ++++ albumin, numerous hyaline casts, and a few fat droplets. The hemoglobin concentration was 70 per cent (Tallqvist). The red cell count was 3.4 million, and the white cell count 12,000, with 81 per cent polymorphonuclears, 13 per cent lymphocytes, and 6 per cent large mononuclear cells.

Hospital Course A few hours after entry the pain extended from the right leg to the left leg, the pelvis and back, and was not relieved by morphine. The following morning both legs and the lower abdomen were blue, with a definite line of demarcation at the level of the umbilicus. The patient became comatose and died in respiratory failure.

Clinical Diagnoses Chronic nephritis with edema (nephrosis), phlebitis of the right leg.

Postmortem Diagnoses Amyloid and lipoid nephropathy, generalized edema, hydroperitoneum and hydrothorax, amyloidosis of the kidneys, spleen, liver and adrenals, terminal pneumonia, pulmonary congestion and edema, liver necrosis, fibrous pleuritis, left, scars in mesentery.

The kidneys were described as follows:

"Right kidney weighs 295 grams, left 300 grams. The capsule strips with ease. The kidneys themselves are rather soft and somewhat mushy to palpation and are much larger in size than usual. Section through the substance of the kidney shows there is escaping a large amount of fluid. This is apparently clear in color. There is a definite rolling of the margins of the kidney, showing considerable amount of edema. The cut surface of the kidney shows a very striking picture, in that throughout the cortex and medulla and somewhat through the pyramids, there is a diffuse, yellowish, somewhat granular appearance of the kidney tissue. This presumably is chiefly fat, so that in this kidney there apparently is a considerable amount of fatty change within the tubules. Kidneys are somewhat paler in color than is usually found. There is no gross evidence of scarring, either coarse or finely granular in type. The amount of fat in the pelvis of the kidneys does not appear to be greatly increased.

"Microscopic examination showed the kidney substance to be edematous. The tubules in many instances are dilated, and in spite of the short time elapsing between death and the postmortem examination (one hour), there is considerable degeneration of the tubular epithelium. Occasional scars are seen in the cortex with connective

tissue increase and inflammatory cell infiltration, which consists largely of lymphocytes. An occasional hyalinized glomerulus is seen. However, the most important lesion seems to be the marked deposit of amyloid along the capillaries in the glomerular tufts and the fatty degeneration in the glomerular epithelium. In addition, there is evidence of acute hyaline degeneration of small blood vessels and capillaries. An occasional cast is seen in the tubular spaces. Several clumps of fat-laden phagocytes are seen."

This case has been presented in the literature before by Christian,¹⁶ primarily as a case of nephrosis due to idiopathic amyloidosis, and as such, has escaped the attention of most writers on amyloidosis. As Christian pointed out, up to that time the nephrotic syndrome was associated only with amyloidosis secondary to chronic suppuration, tuberculosis, syphilis, and certain neoplasms, and the occurrence of nephrosis and primary amyloidosis was not recognized. Dr Christian also suggested that the amyloidosis in this case may have been the result of the treatment of the nephrosis with high protein diets and thyroid.

The duration of symptoms in this patient was three years, which is slightly longer than the usual average of two and a half years for primary amyloidosis. According to Fishberg,¹⁵ most patients who develop secondary amyloidosis of the kidney die within six months to a year.

The diagnosis of primary amyloidosis of the kidney is important, since patients with nephrosis may recover, whereas those with extensive primary amyloid disease probably never do. There are reports of recoveries in secondary amyloid disease when the causes of the amyloidosis are cured or removed, but we have been unable to find any mention in the literature of cures and recoveries in the primary disease.

SUMMARY

Out of 120,785 admissions and 41,551 autopsies, there were 23 cases of proved amyloid disease, of which only three were found to be primary. One of these simulated sclerotic coronary artery disease with heart failure, a second terminated in subacute bacterial endocarditis, and the third gave the clinical picture of the nephrotic syndrome.

Although the diagnosis of primary amyloidosis is difficult, it should be suspected for prognostic reasons.

We are indebted to Dr Orville T. Bailey of the Pathology Department of the Peter Bent Brigham Hospital for his kindness in interpreting the pathologic data discussed and for allowing us to use his photomicrographs.

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CASE REPORTS

THROMBOSIS OF THE AXILLARY VEIN *

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THE literature on the subject of thrombosis of the axillary vein is rather scant. The first description of this as a clinical entity was made in 1884 by Von Schrotter¹ who expressed the opinion that thrombosis of the axillary vein followed an effort which resulted in a sudden stretching of the vein and compression of its walls. The damage thus produced in the vessel wall resulted in a localized phlebitis. In 1920, Cadenat² reviewed the literature and collected 27 reported cases. Gould and Patey³ added eight cases of their own in 1928. Paggi⁴ in a review in 1933 was able to collect 74 cases for study. One year later Matas⁵ added his case and summarized 100 cases which had been reported.

CASE REPORT

A 20-year-old female was taken ill with an upper respiratory tract infection six weeks before she came under observation. This lasted about one month during which time she had a non-productive cough but had no elevation of temperature. Two weeks before admission, she noticed that her right upper extremity appeared swollen and was heavier than the left. The swelling gradually increased. At no time during the six week period did she complain of pain or have any discomfort aside from the fact that she could not fit her right arm into a dress and noticed that her skin was "becoming tense."

TABLE I
Measurements Obtained at Various Levels on Two Occasions

	1/22/38		2/15/38	
	Right	Left	Right	Left
Just below axilla	28 cm	25 $\frac{3}{4}$ cm	30 cm	26 cm
Above elbow	24 $\frac{1}{2}$ cm	22 cm	23.2 cm	21.5 cm
Below elbow	23 $\frac{1}{2}$ cm	22 cm	24.0 cm	22.0 cm
Wrist			15.5 cm	15.0 cm

Her family history was non-contributory. The past history was significant in that three years before coming under our observation, while partaking in a track meet, the patient ran into a stone wall, crashing her right elbow and shoulder against the wall. The arm became swollen and painful within a few hours. She was taken to a hospital where the arm was immobilized in flexion for three days. The swelling and pain gradually subsided, and after several days she made a complete recovery.

At the age of 11 the patient had had rheumatic fever which left no sequelae. Examination revealed a well developed and well nourished white female lying in bed in no apparent distress. The right upper extremity had a purple reddish hue.

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There was fullness in the right infraclavicular region extending toward the head of the humerus. The remainder of the arm was swollen from the axilla to the tips of the fingers. The natural folds of the skin of the forearm were obliterated. The skin was tense, but did not pit on pressure. There was no limitation of the range of motion of the arm. The radial pulse was palpable but the transmitted impulse was slightly diminished. Veins were visible extending from the right sternoclavicular junction to the forearm. The axillary lymph nodes were not enlarged. The arterial filling time was the same on both sides. The pertinent negative findings were absence of a "Horner's collar," no tracheal tug or fixation, no broadening of the mediastinum, absence of tenderness above the right clavicle, and absence of a cervical rib. The remainder of the physical examination was entirely normal.

Comparative measurements of corresponding levels of the two arms are shown in table 1.

Laboratory data: hemoglobin 81 per cent, red blood cells 4,010,000, white blood cells 13,050, polymorphonuclear neutrophils 90 per cent, lymphocytes 7 per cent, eosinophils 1 per cent, basophils 2 per cent. The Wassermann and Kline tests were negative. Urinalysis was normal. Urea nitrogen was 11.5 mg per cent. The red cell sedimentation rate was within normal limits on three occasions. Bronchoscopy failed to reveal the presence of intrinsic or extrinsic lesions in any of the bronchi. There was no evidence of paralysis of the vocal cords. In order to study the effects of obstruction to the venous flow on the products of metabolism, tests were carried out as recorded in table 2.

TABLE II
Comparison of Products of Metabolism in the Blood of Both Arms

	Right	Left
Oxygen content of blood (venous)	12.3 vol per cent	14.8 vol per cent
Sugar	97 mg per cent	97 mg per cent
Carbon dioxide combining power	64.4 vol per cent	66.3 vol per cent
Circulation time	10.2 sec	8.2 sec
Venous pressure	24.5 cm blood	12.0 cm blood

Studies of the venous oxygen content, sugar, and carbon dioxide combining power were made on the blood obtained from each arm and the circulation time and venous pressure were determined. The blood sugar was the same in the blood of both arms. The oxygen content and the carbon dioxide combining power were slightly lower in the blood of the left arm. The circulation time (calcium method) was slightly prolonged on the right side, and the venous pressure although increased in both arms, was twice as high on the right side as it was on the left side. Roentgen-ray examination of the heart, lungs, esophagus and both shoulder regions failed to reveal the presence of any abnormality in size, shape, or position of these structures.

A study of the venous structures (figures 1 and 2) of the right arm by means of a contrast substance injected into the median basilic vein at the elbow revealed a pronounced tortuosity of one of the arm vessels which passes up to the shoulder. No contrast substance could be seen entering the subclavian vein.

A diagnosis of thrombosis of the right axillary vein was made. During the course of her hospital stay, the patient was afebrile. She remained under observation about five months. By the end of this time, the right upper extremity had returned to its normal size. There was a free range of motion of the entire arm. The veins which were prominent on admission were noted to persist until the patient was discharged.



FIG 1 Contrast substance injected into the median basilic vein at the elbow Note the pronounced tortuosity of one of the vessels of the arm which passes to the shoulder



FIG 2 No contrast substance could be seen entering the subclavian vein.

Anatomy The axillary vein is of large size and is the continuation upward of the basilic vein. It commences at the lower border of the tendon of the teres major muscle, increases in size as it ascends by receiving tributaries corresponding to the branches of the axillary artery and terminates immediately beneath the clavicle at the outer border of the first rib, where it becomes the subclavian vein. It is covered in front by the pectoral muscle and the costocoracoid ligament and lies on the thoracic side of the axillary artery. Near the lower margin of the subscapularis muscle, it receives the venae comites of the brachial artery and near its termination, the cephalic vein. This vein is occasionally connected with the external jugular or subclavian veins by a branch which passes from it upward in front of the clavicle. The vein is provided with a pair of valves opposite the lower border of the subscapularis muscle. Valves are also found at the termination of the cephalic and subscapular veins. Other tributaries are the long thoracic vein and the costoaxillary veins which come from the first six intercostal spaces and convey the blood from the intercostal veins to the axillary.

Etiology and Pathology The lack of autopsy material has proved a distinct handicap in determining the pathogenesis of this disease. Many theories attempting to explain the etiology of the thrombus have been advanced. Some of them will be reviewed briefly. The history suggests that trauma of some type is responsible for the thrombosis of the axillary vein, and most authors are agreed as to the significance of trauma in the production of this condition. Lowenstein⁶ apparently made the first serious attempt to study the anatomic structures in the axillary area with reference to this problem. By means of a series of anatomic dissections of 37 cadavers, he found that with the arm in the abducted position the costocoracoid ligament, together with the subclavius muscle, made an indentation in the axillary vein. He concluded that these structures were responsible for trauma to the distended vein when the arm was in marked abduction or extension during muscular effort. Venous stasis or circulatory slowing is produced by the forced expiration that accompanies effort. Under these circumstances, pressure on the vein by the costocoracoid ligament and by the subclavius muscle could be sufficient to effect changes in the vascular endothelium capable of producing thrombosis of the axillary vein.

Gould and Patey⁸ confirmed this observation by injecting plaster of paris into the axillary veins of cadavers, with the arm flexed in the abducted position, they found, in one subject, that there was a definite groove in the axillary vein corresponding to the course of the costocoracoid ligament. In two other cases they observed a broad, deep groove which had been produced by the subclavius muscle. They demonstrated a competent bicuspid valve in this area. These observers were of the opinion that the subclavius muscle was responsible for the trauma to the vein and resulted in rupture of the valve at the junction of the subclavian and axillary veins, and that this was the fundamental pathologic basis for the formation of the thrombus. Most authors^{7, 8, 9} agree that trauma was the etiologic factor in axillary thrombosis. The mode of onset, its predilection for young healthy men and the involvement of the right arm are in favor of this theory.

On the basis of roentgenographic and autopsy studies, Veal and McFetridge¹⁰ reported that the constriction of the vein occurred not as was previously believed over the first rib beneath the subclavius muscle but below the head of the humerus and against the subscapularis muscle. Stretching of the vein

takes place within that part of the vein proximal to the point of constriction below the head of the humerus. Although these facts may be true of cases with marked trauma, it still does not explain the cases in which the accidents are too trivial or those rare spontaneous cases without history of injury^{11, 12, 13}

According to Matas⁵ infection cannot be considered as a constant basis for the thrombosis. He cited 27 cases in which the thrombus was removed, in seven of these the material was subjected to culture. In four cases the cultures were sterile, in the other three cases one yielded *Streptococcus viridans*, the second, *Staphylococcus albus* and colon bacillus, and the third, streptococcus. Changes in the vessel wall were also present, indicating a severe inflammatory type of septic phlebitis. The clinical history, the absence of a rise in temperature and the absence of other evidences of toxemia in many cases spoke against an infectious etiology of this entity.

Syphilis, though often mentioned and suggested as a causative factor, was stated by Lowenstein⁶ to be "as rare as syphilitic arteritis is common."

Taylor,¹⁴ in describing a case of primary thrombosis of the subclavian vein, was of the opinion that an idiosyncrasy in size or position of some anatomical structure, such as bone, ligament or muscle, might be a predisposing factor in all cases of thrombosis from effort. He held that the axillary vein was not subject to pressure, but that thrombosis in the axillary vein might have its origin in the subclavian vein which with the artery, could be compressed by certain movements involving much play at the shoulder girdle, as, for instance, in rowing.

DIAGNOSIS

Reviewing the cases of various authors, one finds that the patients were young, robust, muscular individuals, engaged in heavy work, and that males were affected as in the cases reported by Rosenthal,¹⁵ Cadenat,² Finkelstein,¹⁶ Winterstein,¹⁷ Clute,¹⁸ and others. The right arm was more often involved than the left. Those whose left arm was involved either were left handed, had thrown an unusual strain on the arm,¹⁹ or had sustained an injury to the left side of the chest.²⁰

The diagnosis is based on the following factors. There is usually a history of an accident or an injury by strain although occasionally it may develop spontaneously. Swelling of the arm occurs immediately or several hours or days after the sudden muscle strain or repeated muscular effort. The swelling spreads over the entire arm without any rise in body or local temperature, and without local inflammatory symptoms or any constitutional reaction. The skin has a cyanotic hue. Venous collaterals develop on the affected arm and over the anterior part of the chest. A tender cord is present in the axilla, although this is not a constant finding. Venous pressure in the veins of the affected arm is increased. The venous oxygen content on the affected arm is lowered.¹⁷ The blood flow from the basilic vein on the affected side is increased as compared with the normal side.¹¹ The blood pressure and oscillometer readings in the affected arm may vary slightly from the opposite arm by showing either a slight increase or a diminution. Visualization of the veins with opaque medium reveals the presence of numerous collaterals, distended venous valves, and stasis of the dye in the vessels. Infra-red photography visualizes numerous superficial veins in the affected arm, axilla, and over the chest.

PROGNOSIS

The prognosis as to life is good. The duration of the disability varies from a few months to a year or more because of the persistence of edema. Recurrences have been reported. The rarity with which embolization occurs in axillary vein thrombosis is indicated by the fact that Matas⁵ reported but one case of pulmonary embolism in his excellent review of the literature. This occurred in a 70 year old woman who sustained a fracture of the neck of the humerus. The pulmonary embolus was found at autopsy. Relapse is often provoked by the same sort of effort which was responsible for the initial attack. Patients should always be advised against performing the same type of motion.

TREATMENT

Thrombosis of the axillary vein is best treated by complete rest, elevation of the extremity, and local application of heat. Rest and elevation should be maintained until the edema has subsided and an adequate collateral circulation has developed. Resumption of activity should then be gradual. Veal²¹ does not feel that the results obtained following surgical intervention have justified further attempts to relieve the acute symptoms.

SUMMARY

A case of idiopathic axillary vein thrombosis with recovery is reported.

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A CASE OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD WITH INTERESTING HEREDITARY FEATURES *

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ON January 27, 1938, a man, aged 24, was brought to the Neurological Institute of New York, apparently moribund, suffering with subacute combined degeneration of the spinal cord secondary to pernicious anemia. His mother and paternal uncle had had the same disease. This hereditary background, the abnormally early onset of the illness, and the unusually good response to therapy have prompted the presentation of this case report.

Hurst,¹ Meulengracht,² Johannessohn,³ Tscherning,⁴ Ungley and Suzman,⁵ and others have presented instances of subacute combined degeneration occurring in more than one member of a family. Wilkinson and Brockbank⁶ in 1931 reviewed the literature, collecting (1) 125 families in which two or more members were affected with pernicious anemia with or without the complication of subacute combined degeneration of the spinal cord, (2) 51 families in which pernicious anemia and achlorhydria existed simultaneously, and (3) 14 families in which achlorhydria was found without pernicious anemia. They added to the first group 14 cases from their own material, to the second group 8, and to the third group 3.

CASE REPORT

D C, a 24-year-old white male, employed as a clerk, was admitted to the Neurological Institute of New York January 27, 1938. He had had Sydenham's chorea at age 12, after which he was told that his heart had been damaged. During the last eight months of 1935, at the age of 22, he lost a total of 48 pounds of body weight, was easily fatigued, and noticed progressive muscular weakness and palpitation of the heart. Vomiting and extreme weakness of three days' duration necessitated his hospitalization in Brooklyn January 29, 1936. His skin was then pale lemon yellow, the cardiac apex was outside the midclavicular line, and a double murmur was audible over the mitral area. The heart rhythm was regular. The liver and spleen were not palpable. There were 2,000,000 erythrocytes per cu mm of blood, with moderate poikilocytosis and

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From the Neurological Institute of New York, New York City

anisocytosis The hemoglobin was 60 per cent (method not stated) and the color index 1.5 The leukocyte count was 7,250 per cu mm, of which 75 per cent were polymorphonuclear neutrophils, 3 per cent eosinophils, 1 per cent basophils, 20 per cent small lymphocytes, and 1 per cent monocytes No gastric analysis was done A diagnosis of pernicious anemia was made, and the patient was given "Jeculin" (a proprietary liver and iron preparation), 4 c.c. by mouth three times daily, and an iron preparation by hypodermic (exact preparation and dosage not known)

He gained weight, but never felt really well After January 1937 he was weak and lethargic, and his tongue was often sore There were occasional episodes of palpitation of the heart In September 1937 he noticed numbness and tingling in the toes of both feet Marked weakness of both legs set in Intermittent spontaneous jerking motions of both legs began November 1937, accompanied by unsteady gait and urinary frequency with urgency, nocturia, and occasional dribbling incontinence He became bedridden and was hospitalized in Brooklyn December 27, 1937 His blood then contained 4,010,000 erythrocytes per cu mm, with hemoglobin 76 per cent (method not stated), the color index was 95 There were 6,900 white blood cells per cu mm, of which 72 per cent were polymorphonuclear neutrophils and 28 per cent large lymphocytes Other laboratory tests, including examination of the spinal fluid, were normal, but no gastric analysis was performed No definite diagnosis was made The only antianemic medication continued to be "Jeculin" by mouth and an unspecified type of iron preparation parenterally The patient became rapidly more ill About January 24, 1938, he became disoriented and refused food, fluids, and medications He was transferred to the Neurological Institute of New York January 27, 1938

On admission there he was disoriented and negativistic, hallucinated actively, and expressed ideas of persecution His skin was pallid and subicteric He was mildly emaciated and markedly dehydrated His temperature was 101.4° F rectally, blood pressure 130 mm Hg systolic and 70 mm diastolic, and pulse 122 The tongue was smooth and raw at its edges and tip, but not atrophic over the dorsum The cardiac apex was in the sixth interspace 2 cm beyond the midclavicular line There were presystolic and systolic murmurs at the apex, transmitted into the left axilla The rhythm was regular There were no basal lung râles and no ankle edema The liver and spleen were not palpable From an area of inguinal intertrigo numerous superficial pustules had been seeded over both legs, buttocks, and forearms At no time was he observed to move either leg at all Both arms were moved equally well, but weakly His legs were markedly spastic, his arms mildly so There was marked bilateral hyperreflexia, with patellar and ankle clonus and Babinski and Hoffmann responses Sensory examination was impossible

His blood on admission contained 3,160,000 erythrocytes per cu mm, showing marked macrocytosis, poikilocytosis, and some polychromatophilia The hemoglobin was 78 per cent Sahli and the color index 1.26 There were 11,400 leukocytes per cu mm, of which 72 per cent were polymorphonuclear neutrophils and 28 per cent lymphocytes The urine showed a faint trace of albumin and occasional pus cells, but was otherwise negative The erythrocyte sedimentation rate was 107 mm in one hour The blood urea nitrogen was 18 mg per 100 c.c., and the blood sugar, fasting, 93 mg per 100 c.c. The cerebrospinal fluid contained 163 red blood cells (the result of trauma) and 3 white blood cells per cu mm, and 38 mg of protein per 100 c.c. The spinal fluid Wassermann reaction was negative in all dilutions, and the colloidal gold curve was normal The manometric response to jugular compression was normal Gastric analysis, done on two occasions, both with histamine, showed no free acid in any specimen Blood Wassermann reaction, blood cultures, blood agglutinations for typhoid, paratyphoid, and Brucella, as well as roentgen-rays of the spine, skull, sinuses, and teeth, were negative The electrocardiogram showed no important findings

High-caloric, high-vitamin tube feedings with added ground liver were necessary twice daily during the first week. The patient received Lederle's concentrated liver extract, 3 c c intramuscularly, daily, and thiamin chloride 10 mg by hypodermic daily for the first 50 days. Thereafter, he received Lederle's concentrated liver extract 3 c c intramuscularly three times weekly, with thiamin chloride, 8 mg by mouth daily. In addition, he received ventriculin 10 gm three times daily from February 25 until he was discharged April 5. Dilute hydrochloric acid was given with meals. Care of the skin was stressed. He was given daily massage to the legs and arms, together with passive, and later, active exercises. Reeducational walking exercises were instituted at the earliest possible time, 21 days after admission, and were continued until discharge.

After an initial 10 day period of fever ranging as high as 103° F, the patient was fever free. Psychotic symptoms disappeared eight days after admission, he became cooperative and rational, but, in marked contrast to his previous shy, withdrawing personality, he was loud, rambling, and discursive in speech, and forward in manner. Seven days after admission, and one day before cessation of psychotic symptoms, there was a reticulocyte response of 13.8 per cent, the erythrocyte count on that day was 2,840,000 and the hemoglobin 72 per cent Sahli. Nine days after admission the reticulocyte count was still 13.4 per cent, the erythrocyte count had risen to 3,220,000 and the hemoglobin to 78 per cent. Subsequently the blood picture improved steadily. The reticulocyte count remained as high as 12.6 per cent until 13 days after admission and was still 5.4 per cent 32 days after admission, when the erythrocyte count had reached 4,240,000 and the hemoglobin was 90 per cent Sahli. Forty-three days after admission the erythrocyte count had attained 5,040,000, and the hemoglobin 102 per cent Sahli. On discharge from the hospital April 5, 1938, the erythrocyte count was 5,180,000 and the hemoglobin 104 per cent Sahli. Interestingly, the leukocyte count averaged about 12,000 until the patient's discharge, although he was afebrile and all evidences of infection had been eradicated.

Eight days after admission and one day after the onset of marked reticulocyte response, incontinence of urine and feces practically ceased, and the patient began to exhibit slight muscular power in both legs, especially in the proximal musculature. Sensory examination, now possible for the first time, found no impairment of sensibility to painful or tactile stimulation, but vibratory and position sense were lost in both legs. Motor power now improved rapidly. Twenty-two days after admission it was estimated as being 50 per cent for all motions of the legs and 100 per cent for all motions of the arms. Walking exercises were instituted on the twenty-first day. Thirty-seven days after admission muscular power was assessed as normal for all motions tested, in all extremities. Thirty-nine days after admission the patient was able to walk the length of the gymnasium, on a rubber mat, supported by a cane, the gait was clumsy, spastic, and ataxic. Fifty-four days after admission the patient was able to walk short distances without a cane, with little spasticity or ataxia. On discharge from the hospital April 9, 1938, 72 days after admission, he was able to walk the length of the ward without his cane.

When the patient was reexamined at the time of his discharge, none of the extremities showed more than slight spasticity. He fell in the Romberg position with the eyes closed, and swayed moderately in the same position with the eyes open. The heel-to-knee test was performed in a mildly ataxic manner on both sides, but the finger-to-nose tests were well done. Vibratory and position sense were still absent in both legs. Marked hyperreflexia continued, with transient patellar and ankle clonus, and Babinski responses. The rest of the systemic examination remained essentially unchanged, save for complete elimination of furunculosis and marked improvement in general well-being.

Treatment was continued in the hematology outpatient department, where the patient received intramuscular injections of Lilly's liver extract, 6 c c weekly. He continued to take dilute hydrochloric acid by mouth, and 300 International units of thiamin chloride by mouth daily. May 18, 1938, less than four months after his admission to Neurological Institute, he had discarded his cane and was able to walk as much as 14 blocks at one time. He was still very unsteady in the Romberg position. He returned to his former clerical job, which he has continued to fill adequately. His blood count was maintained above 5,000,000 at all times. On April 19, 1939, there were 5,600,000 erythrocytes per cu mm, with hemoglobin 17.5 gm. The leukocyte count was then 8,550 per cu mm, with 69 per cent neutrophils, 4 per cent eosinophils, 20 per cent lymphocytes, and 7 per cent monocytes.

When reexamined January 14, 1939, one year after his admission to Neurological Institute, the patient was mentally clear, but still garrulous and discursive. He was florid, somewhat obese, and in obvious good health. He said he was able to walk well without a cane, even on an icy street, and noticed only that he was unable to run. Gait was adroit and confident, with minimal spasticity and tendency to over-adduction of either leg as it was moved forward in walking. The Romberg was negative, heel-to-knee and finger-to-nose tests were well performed. Hyperreflexia, clonus, and Hoffmann and Babinski responses were still present bilaterally. Position sense was still absent in all the toes, and vibratory sensibility was absent in the hips, sacrum, and legs.

He was seen again May 24, 1939, approximately 16 months after he had been admitted to Neurological Institute. His functional improvement had been maintained. Gait was excellent. Exaggerated deep reflexes, with transient clonus, continued. There was possibly slight restoration of position and vibratory sensibility in the right foot.

Discussion of Hereditary Background. The patient's father was of "Scotch-Irish" descent, the mother of Swedish stock. The mother and one paternal uncle had pernicious anemia with subacute combined degeneration of the spinal cord. A search through three generations of both families located no other cases of anemia or locomotor difficulty. The paternal family is now resident in Alberta, Canada, and could not be examined. The maternal sibling group (five in all) lives in Brooklyn. They permitted the performance of blood counts, but would not submit to gastric analysis. The lowest erythrocyte count was 4,780,000 per cu mm. The lowest hemoglobin was 82 per cent. The stained blood smears showed no significant variation from normal. The patient's only sibling, an older sister, aged 26, submitted to both blood count and gastric analysis. The former showed an erythrocyte count of 4,800,000 with hemoglobin 88 per cent Sahli, and color index of 91. There were 11,700 leukocytes per cu mm. The fractional gastric analysis (histamine method) showed large amounts of free hydrochloric acid in each specimen, the maximum being 120 degrees at the end of 30 minutes.

At the age of 41 (in 1930) the patient's mother had developed rapid, progressive anemia, with paralysis of both legs, and died within six weeks of the onset of symptoms. Unfortunately little more is known of the history of her case. When she was admitted to the Hackensack Hospital, Hackensack, New Jersey, her blood count showed 1,150,000 red blood cells per cu mm, with hemoglobin 20-25 per cent (method not stated). The white blood cells numbered 8,600 per cu mm. The urine showed one plus albumin and occasional

white blood cells, but was otherwise negative. The blood Wassermann reaction was 4 plus. The autopsy diagnosis was pernicious anemia.

A paternal uncle at the age of 44 began to tire easily, and noticed that his skin was yellow in color. A few months later there set in throbbing midlumbar pain, and soon thereafter lower abdominal numbness with progressive loss of power of the legs, and ataxia. He was admitted to the University of Alberta Hospital * July 16, 1934. Examination at that time showed marked pallor, with icterus. The patient was irritable and somewhat facetious. Otherwise the general systemic examination was negative. There was weakness of both legs

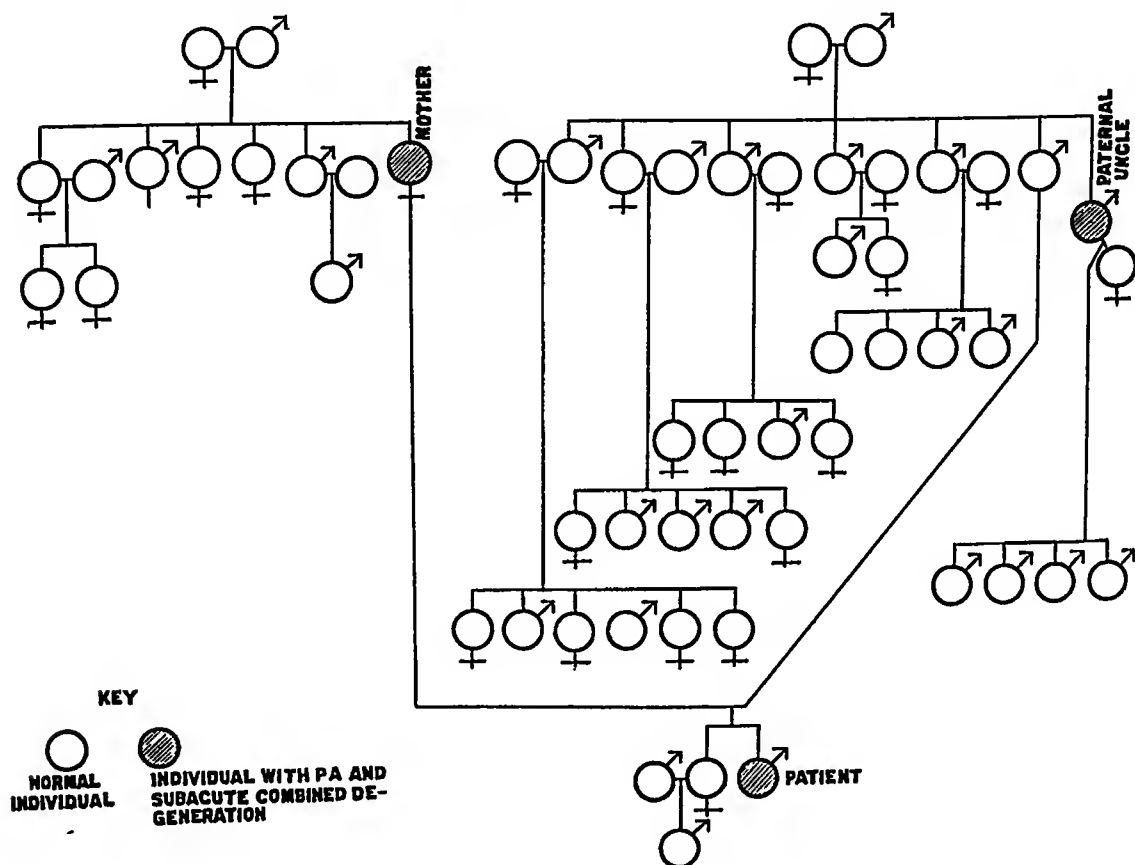


FIG 1 Family tree

with spasticity. Strength in the arms was normal. Ataxia was present in arms and legs. Vibratory sensibility was impaired in both legs. The position sense was apparently not tested. The deep reflexes were exaggerated throughout, with bilateral ankle and patellar clonus. There was a bilateral Babinski response. The blood count at that time showed 2,280,000 red blood cells with 8.5 gm hemoglobin and color index 1.3. There was poikilocytosis, anisocytosis, and macrocytosis. There were 3,100 white blood cells per cu mm. The blood Wassermann reaction was negative. Gastric analysis showed no free acid in any specimen. Spinal fluid examination was negative. The patient was placed on liver therapy (exact details not known). We do not know his subsequent blood counts, but he is said to have improved markedly and to be able to walk at present with the aid of two canes.

* To which we are grateful for the following report

DISCUSSION

It is unusual, but not entirely unheard of, for pernicious anemia to set in so early in life. Fortunately, such marked progression of symptoms in these days is very rare, because adequate liver therapy (i.e., liver by intramuscular injection) is usually initiated early in the course of the illness. This patient received nothing but oral liver preparations until he was practically moribund. This case again emphasizes the advisability of maintaining the blood count at 5,000,000 or above in order to make less likely the occurrence of neural symptoms. Subsequent to the initial diagnosis of pernicious anemia this patient's blood count was elevated in an apparently satisfactory manner. Neural symptomatology advanced rapidly while the red blood cell count was as high as 4,010,000 with hemoglobin of 76 per cent (December 1937). This case also belies the pessimistic teaching maintained by many that one can hope only for arrest of neural symptoms, but not for any substantial return to normal, despite therapy. Attention is called to the massive parenteral liver therapy employed in this case and to the administration of thiamin chloride parenterally, further, to the early and vigorous employment of physiotherapeutic measures, i.e., massage and passive exercise, followed as soon as possible by active exercises and later by reeducational walking exercises. It was interesting that psychotic symptoms were substantially cleared before any rise in red blood cell count occurred, but one day after a substantial reticulocyte response took place (13.4 per cent).

Pernicious anemia, with subacute combined degeneration of the spinal cord, was present in one member each of the preceding generation in both the maternal and paternal families. The patient's only sibling was free of any of the stigmata of pernicious anemia, including achlorhydria. Pernicious anemia occurred after the age of 40 in both of the affected members of the preceding generation, but in the patient it occurred in the early twenties. Although only three cases are involved, there is a suggestion that the illness tends to occur at earlier ages in successive generations. This tendency was also evident in the family reported by Ungley and Suzman.⁵ The scanty data here presented suggest hereditary transmission of the disease as a Mendelian recessive character.

SUMMARY

A young man developed pernicious anemia at the age of 22 years and subacute combined degeneration of the spinal cord at the age of 24, after inadequate, purely oral, liver therapy. Both his mother and a paternal uncle had had pernicious anemia and subacute combined degeneration. The familial background is presented in some detail. The patient entered the hospital moribund, completely paralyzed in both legs, and psychotic. He was placed under intensive therapy, which included massive doses of intramuscular liver and parenteral thiamin chloride, followed by massage, passive and active exercises, and as soon as at all practicable, reeducational walking exercises. Fifty-four days after admission the patient had attained the ability to walk short distances, unsupported, even with a cane. Four months after admission he had returned to work and had improved to the point of discarding his cane entirely, walking as much as 14 blocks at one time. This improvement has been maintained. When the patient was last seen, 16 months after admission to the hospital, gait

was for all practical purposes normal. Hyperreflexia, pathological reflexes, and impairment of vibratory and position sense in the legs persisted. It is suggested that this remarkable improvement was due to the employment of doses of intramuscular liver much larger than ordinarily used, and maintained over a long period of time, to the employment of substantial doses of parenteral thiamin chloride, and the early initiation of vigorous physiotherapeutic and reeducational measures. Continued improvement, without relapses, following the patient's discharge from the hospital was greatly aided, we believe, by maintenance of the patient's blood count above 5,000,000 red blood cells per cu mm with appropriate doses of intramuscular liver. Pernicious anemia and subacute combined degeneration may have an hereditary basis, with transmission after the manner of a Mendelian recessive character. The disease may have a tendency to occur at progressively earlier ages in successive generations.

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FRIEDREICH'S ATAXIA¹

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IN 1861 Nicolaus Friedreich first described a primary hereditary spinal cord disease which caused progressive ataxia of first the legs and then the arms, but without paralysis of the sphincters or disturbance of the senses. He correctly assigned the major pathologic lesions to the region of the posterior and lateral columns, designating it a chronic degenerative atrophy, but thought it closely related to tabes dorsalis, a belief which was later disproved. Following this several similar cases were reported and later many variations from the usual type were described, such as those in which cerebellar involvement predominated, a form now classed as Marie's cerebellar ataxia.

Friedreich's ataxia is one of the many unusual neurological diseases that are both rare and interesting. Characteristically it has its onset early in life, between the ages of five and 14, although in one family reported (Brown) the

* Received for publication October 23, 1937

† Deceased

youngest member was six and the oldest 39 when the earliest manifestation of the disease appeared Jenrassik has reported a case beginning in a patient 50 years old ¹⁰

The syndrome progresses slowly and relentlessly without regard to treatment There are frequently long remissions, however, and the patient may reach old age ¹⁰

The affected individual has, so far as can be told, an inherent neurone deficiency with a tendency to specific central nervous system degeneration passed



FIG 1

on by some previous generation, although a definite family history is by no means invariably found

There are many causes for pathologic changes involving the posterior and lateral columns of the spinal cord simultaneously Pernicious anemia, leukemia, aplastic anemia, diabetes, pellagra, syphilis, and chronic ergot poisoning are among the more common types However, these are owing to diseases not primary in the central nervous system, none of them is known to produce any deformity of the feet, and their differentiation from this disease is usually easy

Amyotrophic lateral sclerosis, according to Boyd, may cause pes cavus, but there should be little cause for difficulty in differential diagnosis The onset of amyotrophic lateral sclerosis is in the upper extremities with atrophy of the

thenar and hypothenar eminences, progressing up the arms toward the shoulders but often leaving intact some muscle groups

The first symptom, stumbling while running or walking, apparently is owing to the progressive onset in the proprioceptive fibers of Goll and Burdach (posterior columns) These columns carry no pain fibers and thus involvement accounts for the presence of some of the characteristic manifestations of tabes

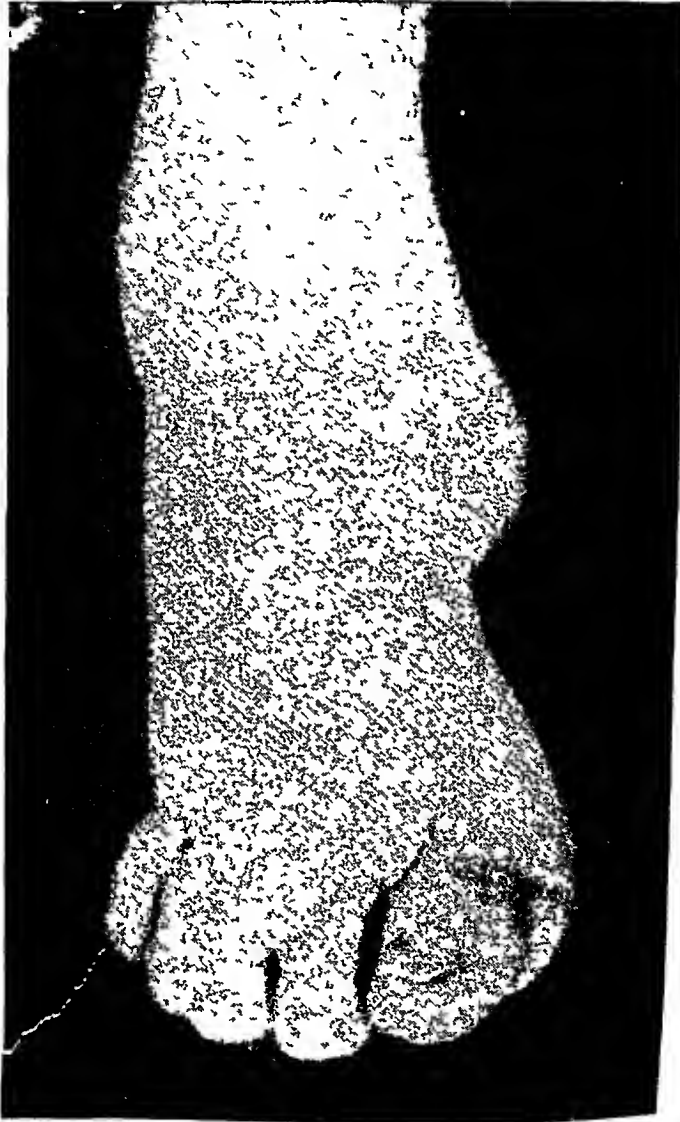


Fig 5 Anterior view of the right foot illustrating the continuous Babinski position of the toes

dorsalis, na
position of
locomotor a
girdle sensat
and spinal flu
To the invol
ely a positive Romberg sign, and loss of sense of motion and
the great toes However, this disease can be differentiated from
luxia by the absence of tabetic crises, Argyle-Robertson pupils,
ns, by absence of the characteristic serologic changes in the blood
and by the difference in gait
vment of the lateral columns is attributed the characteristic

bilateral deformities of the feet with occasional fixation of one or both ankle joints. There is a pes cavus accompanied by a "continuous Babinski sign" with persistent extension of the great toes and plantar flexion of the remaining digits. This makes it impossible to make the usual tests for the presence of abnormal extensor reflexes.



FIG 3 (above) Lateral view of the left foot showing extension of the great toe and moderately well the pes cavus (below) Lateral view of the right foot showing the pes cavus

Late in the course of the disease there is sometimes a loss of the knee jerks owing to degeneration of fibers proximal to the sensory ganglia.

In most cases the direct cerebellar tract is invaded with the production in varying degree of vertigo, increased ataxia, and a 'drunken reel' in the gait. A gross tremor of the upper extremities and head is always present.

There is no pain, and there is no disturbance of superficial pain, temperature, or touch sensations. The mentality remains approximately normal, although this is occasionally disturbed in the terminal stages.

Macroscopically the greatest pathologic change is hypoplasia of the spinal cord, with a reduction in its diameter, involving either the entire length of the cord, or mainly the upper dorsal and cervical regions. In some cases the cerebellum is the seat of the major changes and if so the syndrome is likely to be classed as hereditary cerebellar ataxia, to which Friedreich's disease is closely related. As a rule the columns of Goll and Buidach are the first to suffer,

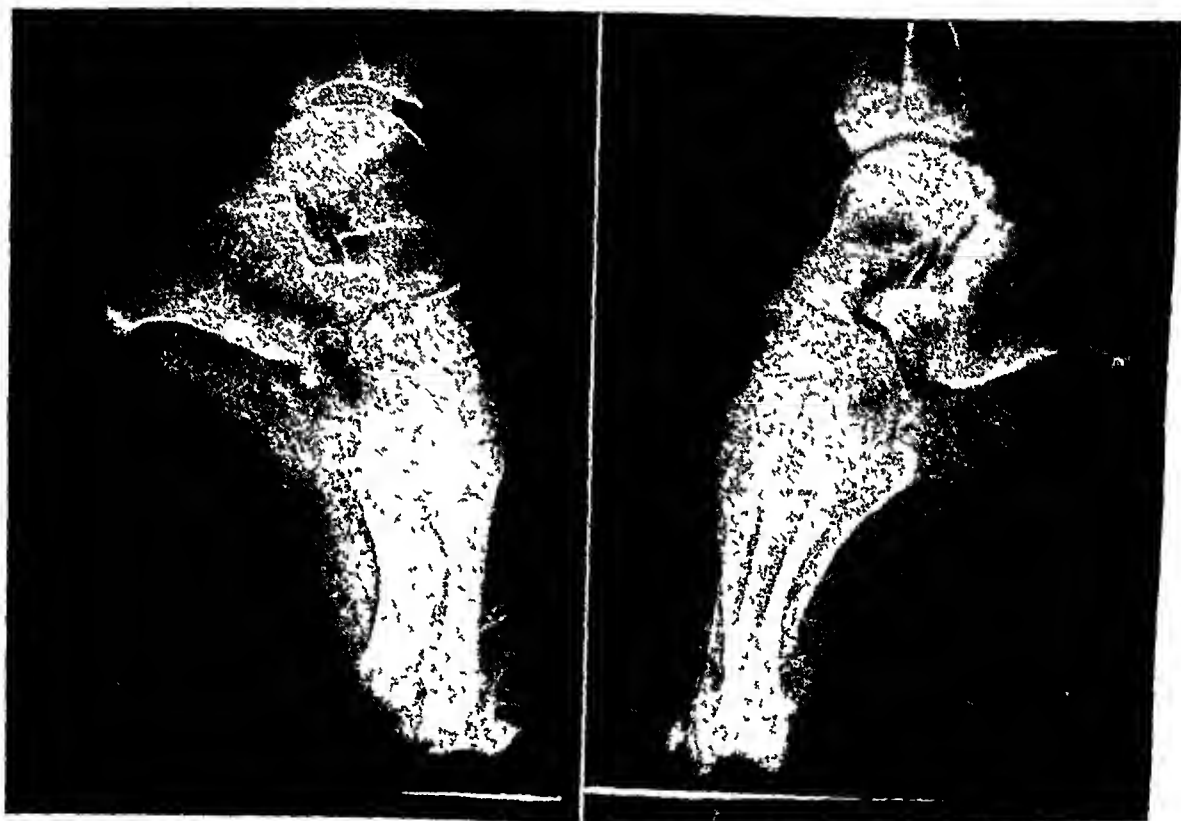


FIG 4 Roentgen-rays of both feet showing the weight bearing lines

followed by the pyramidal tracts, columns of Clark, sometimes the ascending cerebellar pathways, and to a variable degree the cerebellum itself. Various secondary manifestations are thickening and adhesion of the pia mater, particularly near the posterior columns, and thickening of the blood vessel walls.⁴

Microscopically there are numerous whorls of neuroglia in the posterior columns, the pyramidal tracts, the cerebellar paths, and the fibers passing from the posterior roots of the spinal cord to the anterior horn cells (part of the simple reflex arc), which are incident to the degeneration in these areas.

CASE REPORT

Mr H S, whose history is unreliable as to date of onset, time, and sequence of events, is a bachelor, aged 69, who has had a "high instep" since childhood and pes cavus of the right foot since the age of 24 years. He has been able to work but

during the past 12 years walking has become increasingly difficult, and a gross tremor of the fingers, arms, and head has become much worse. He has also had occasional dizziness.

There is a past history of typhoid fever at the age of 10, gonorrhea at 20, and other infectious diseases at unknown ages. Deafness has been evident in the left ear for nine years. Negative Wassermann and Kahn tests were obtained eight years ago.

The family history includes no known cases of paralysis and none of pes cavus, though he does not "know or remember his parents well."

Physical examination revealed an elderly man weighing 200 pounds, with normal color and features. The hair was gray and skin was of normal color and texture. The nose and ears were negative, except for deafness in the left ear. The head was made conspicuous by an almost continuous gross tremor. The pupils were equal and reacted to light and on accommodation. There was no arcus senilis. The eye grounds showed a normal fundus, with moderate tortuosity of the arteries. There was no nystagmus. The mouth was edentulous.

Chest The lung fields were clear to palpation, auscultation, and percussion.

Heart The left border of cardiac dullness was nine centimeters to the left of the mid-sternal line. There was no murmur or irregularity in rhythm. Blood pressure systolic 158, diastolic 90 mm Hg.

Abdomen The panniculus was above the level of the thorax. No abnormal masses or tenderness could be found.

The extremities presented a gross continuous tremor of both upper extremities. The hands were of normal appearance. No abnormality was to be found in the thighs. There was a moderate atrophy of the muscles of the right lower leg, less marked on the left, and some fixation about the right ankle. Temperature and pain sensation were retained on every part of the body. Knee jerks were present, equal and active, although it was impossible to obtain the tendoachilles reflexes. Deep tendon pain was unimpaired, but there was a disturbance of the sense of motion and position as evidenced by the positive Romberg sign, and an inability to tell the position of either great toe when manipulated by the examiner. The finger to nose test was fair, and there was no dysdiadochokinesia. The most striking finding in the extremities was a marked bilateral pes cavus with hyperextension of the great toes and plantar flexion of the remaining digits.

Roentgenograms in this case show, in addition to the pes cavus and dorsal displacement of the proximal phalanges, that the weight was shifted directly to the metatarsals and that the calcanei were supported only by raising the heels of the shoes. No bone abnormality was seen to account for fixation of the right ankle.

SUMMARY

Though the details of the history presented in this case are to some extent unreliable, there has been evident ataxia since childhood, and the patient is now incapacitated to the extent that it requires more than half an hour for him to walk a distance of 200 yards. When walking he leaned slightly forward on two canes with both legs straight, and pulled each foot forward as a step was taken.

There is definitely a lesion involving the proprioceptive fibers and also the pyramidal tracts. A characteristic tremor is present. Occasional attacks of dizziness indicate a probable involvement of the cerebellar pathways.

The retention of the knee jerks is unusual but this is observed in some cases of Friedreich's ataxia. The discrepancies in the history can be ascribed to the

inaccuracies of the patient The characteristic pedal deformities are practically diagnostic

Diagnosis Friedreich's ataxia with onset at some time after puberty

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A CASE OF SPINDLE CELL SARCOMA OF THE BRONCHUS; SUPPLEMENTARY REPORT *

By OTTO S BAUM, M D, GERTRUDE SILVERMAN, M D, RIEVA ROSH, M D,
and RICHARD L RILEY, M D, *New York, N Y*

IN November 1938 one of us (O S B) reported a case of atelectasis of the right lower and middle lobes due to spindle cell sarcoma of the right main bronchus¹ The patient has since died, and this brief supplementary report, with a summary of the autopsy findings, is given for the sake of completeness, as well as because of the nature of the terminal illness A brief summary of the early course of the disease is also given

The patient, R Z, was a 32 year old housewife, first admitted to the Second (Cornell) Medical Division of Bellevue Hospital on March 16, 1938 Six weeks prior to entry she had developed a respiratory illness, diagnosed as "pneumonia and pleurisy" by her physician A persistent low grade fever, cough productive of small amounts of mucoid sputum, sharp right-sided chest pain, and weight loss of 15 pounds characterized the period intervening between the onset and the episode causing admission This was characterized by more severe right chest pain, nausea, and vomiting Salient features of the physical examination were marked deviation of the trachea and mediastinum into the right chest, dullness to flatness, absent breath sounds, and preservation of vocal fremitus over the lower two-thirds of the right chest anteriorly and posteriorly Laboratory findings, including sputum examination for tubercle bacilli, were negative Bronchoscopic examination showed a mass of friable polypoid tissue completely obstructing the right main bronchus just below the origin of the upper lobe bronchus Following the removal of tissue for biopsy and suction

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From the Tuberculosis Service, the Department of Pathology, and the Department of Radiation Therapy of Bellevue Hospital, New York City

an airway was established, aided by the expulsion of a bronchial cast of tissue shortly after bronchoscopy, and the patient re-aerated her right middle and lower lobes within 24 hours. Microscopic examination of tissue removed for biopsy and of the bronchial cast showed a spindle cell sarcoma. Bronchoscopy was repeated 13 days after the first bronchoscopy, at which time the tumor was found to arise on the lateral aspect of the right main bronchus, encroaching on the mouth of the upper lobe bronchus, the orifice of which was transformed into a slit. On the following day deep roentgen therapy was started, treatment being given to the anterior, lateral and posterior aspects of the right chest, directing the center of portal over the center of the lesion.

During the subsequent two and one-half years the patient received therapy at the following periods:

March 31 to June 3, 1938	1950 r units to each portal
March 3 to March 6, 1939	160 r units to each portal
March 20 to June 20, 1939	2150 r units to each portal
	1950 r units right upper lateral chest
November 13 to December 14, 1939	1400 r units to anterior and posterior right chest
June 14 to July 18, 1940	2000 r units to anterior and posterior right chest
September 20 to October 4, 1940	500 r units directing through right supra-clavicular area

Factors used: 200 K V, 20 ma, 50 cm, STD, 9×12 or 10×15 portal, 0.5 cu and 1 al filter output, r per minute 200 r given to each area at a time, and one area treated, alternating daily. All measurements made in air. Output 40.5 r per minute.

Bronchoscopic examinations were performed by Dr. Maxwell Ryan at intervals of approximately three months. In May 1938 the tumor had practically disappeared, only a very small tag of tissue jutted out just below the opening of the right upper lobe bronchus, which was widely patent. This tag of tissue was removed by forceps. In August 1938 there was no visible lesion in the bronchus. In February 1939 there was elevation of the mucosa at the previous site of the tumor, and microscopic examination showed submucosal recurrence of the spindle cell sarcoma. At this time she was admitted to the Tuberculosis Service of Bellevue Hospital for consideration of total pneumonectomy. This was decided against because of the proximity of the neoplasm to the carina, and the patient was referred to the Radiation Therapy Service for further treatment. The sputum at this time was negative for tubercle bacilli.

Roentgen-ray films between March 1938 and August 1939 were considered normal. Beginning August 3, 1939, abnormal findings were noted, consisting of mixed soft and fibrotic infiltration extending from the right hilum into the second anterior interspace, localized by lateral views in the base of the right upper lobe. Subsequent films showed increasing infiltration of the same character, with involvement in the area behind the first anterior intercostal space, where questionable rarefaction was observed. Some retraction of the upper mediastinum into the right chest was first noted in the film of June 6, 1940, on August 16, 1940, nodular deposits were present in the periphery of the right second interspace.

The first abnormal findings in the chest roentgenogram coincided with the onset of a dry hacking cough, associated with occasional sensations of tightness in the chest. Because bronchoscopy in November 1939 showed a small amount of friable tissue at the mouth of the upper lobe bronchus, which bled easily when touched, it was believed that another recurrence had taken place and that the shadows noted in the chest film were due in part to the neoplasm and in part to postradiation fibrosis. Further deep therapy was given cautiously.

During the following year the patient was troubled by a spasmodic unproductive cough and moderate weight loss. Because of these symptoms and of extension of

the process as indicated by roentgen-ray examination a further course of therapy was begun in June 1940

The patient's final admission to Bellevue was on August 29, 1940, when she gave a history of chills and fever up to 104° F for the preceding two weeks, associated with further weight loss, night sweats, and increasing sputum which at first had been mucoid but later assumed a purulent character. Physical examination on admission showed a postradiation induration over the anterior, lateral and posterior aspects of the right chest, and dullness and intense bronchial breath sounds with many coarse râles over the region of the right upper lobe. The patient's temperature varied between 101 and 105° F, and was unaffected by two courses of sulfapyridine and sulfadiazine respectively. Bronchoscopic examination on September 11, 1940, showed retraction of the upper lobe bronchus toward the right. At the posterior proximal border of the mouth of the upper lobe bronchus there was a small spongy mass which bled easily. The mouth of the upper lobe bronchus was patent, but there was relatively little air exchange. Microscopic examination of the spongy mass showed only blood clot. The sputum on September 10, 1940, was negative for tubercle bacilli on direct smear. The white blood count fluctuated between 8,000 and 9,100, with 92 per cent polymorphonuclear leukocytes, predominantly young forms. Sputum culture showed the presence of *Staphylococcus aureus*, *Streptococcus viridans*, and *Micrococcus catarrhalis*. Blood culture was negative. Roentgen-ray examination of the chest showed signs of consolidation of the right upper lung field, a large cavity in the first anterior interspace medially, and a soft patchy nodular infiltration in the third anterior interspace.

It was felt that the patient had developed a suppurative pneumonia of the right upper lobe secondary to the bronchial neoplasm, and she was transferred from the Second (Cornell) Medical Service to the Tuberculosis Service for palliative drainage of what was thought to be an abscess of the upper lobe. She had become hoarse during her hospital stay, and laryngoscopy on October 11, 1940, showed abductor paralysis of the left vocal cord, interpreted as due to a mediastinal lesion involving the left recurrent laryngeal nerve. Radiation therapy had been given on five occasions on this admission, 100 r units being given to the right supraclavicular area each time.

It was a surprise when sputum examination revealed innumerable acid-fast bacilli in the smear, confirmed by several subsequent examinations. An artificial pneumothorax was induced on the right but was abandoned when the upper lobe was found to be densely adherent. The irregular fever persisted, ranging between 102 and 104° F, and the patient rapidly became weaker. Roentgen-ray and physical examination showed evidence of a massive exudative spread into the left lung. For the week prior to death the patient raised increasing amounts of fluid purulent sputum, which now had a foul odor. Death occurred on November 2, 1940, two years and eight months after the first admission to Bellevue Hospital.

Postmortem Examination (Dr Silverman) The significant autopsy findings were as follows:

Macroscopic The skin over the right thorax showed diffuse brownish pigmentation. The marrow of the ribs was pale and firm, particularly on the right side. The right lung was adherent to the chest wall over the upper two-thirds, whereas the lower one-third was collapsed by pneumothorax. There were approximately 100 cc of clear fluid in the right pleural cavity, and 200 cc of serofibrinous fluid in the left pleural cavity. In the anterior superior mediastinum there was an irregular piece of red tissue 3 by 3 by 1½ cm in size, apparently a thymic remnant. The left recurrent laryngeal nerve was free throughout its mediastinal course. The mucous membrane of the trachea and of both main bronchi was very red and somewhat thickened. The walls of the right main bronchus and its upper lobe branch were more granular than the rest, but no constriction or ulceration was noted. At the point of bifurcation of the right

upper and lower lobe bronchi, that is, at the site of the original neoplasm, there was a minute firm nodule. No other evidence of neoplasm was noted. The right upper lobe was composed mainly of a single large irregular cavity, with poorly defined, collapsed walls, containing greenish foul-smelling grumous material, which communicated freely with the lumen of the upper lobe bronchus. There were extensive nodular deposits, 2 to 6 mm in diameter, with evidence of caseation, throughout all the other lobes. In addition there was massive consolidation of the upper portion of the left lower lobe, having the appearance of an acute tuberculous pneumonia. The pulmonary artery going to the right upper lobe was completely occluded by a firmly attached, pinkish-gray thrombus. There were a number of small black mediastinal lymph nodes.

Microscopic The nodule at the bifurcation of the upper and lower lobe bronchi on the right was made up of bundles of apparently fibrous tissue running in various directions, abutting at its base against necrotic tuberculous tissue and older fibrous tissue with a round cell infiltration. Deep-lying vessels showed calcification in their walls (radiation therapy changes).

The lining of the trachea and main bronchi throughout showed metaplasia into squamous epithelium and extensive caseous and proliferative tuberculosis. The wall of the right upper lobe cavity was made up of necrotic lung tissue with no delimiting granulation or fibrous tissue or adjacent inflammatory reaction. There was almost complete necrosis of all adjacent lung tissue. The small arteries showed inflammatory infiltration and destruction of their walls and recent thromboses in their lumina. The wall of the main upper lobe branch of the pulmonary artery was necrotic, probably the result of direct extension of tuberculous caseation from a partly epithelialized bronchus. Sections throughout the remainder of both lungs showed extensive caseous tuberculosis. Lymph nodes below the carina showed proliferative tuberculosis. Section of the tissue from the anterior superior mediastinum showed striated muscle, loose fibrofatty tissue, and lymphoid tissue. The latter showed old hyalinized foci, in places diffuse fibrosis, and isolated epithelioid tubercles with some necrosis and giant cell formation. In the loose fatty tissue there was a single calcified body (old Hassal's corpuscle?) and perivascular cellular infiltration of large lymphocytes and fibroblasts, inflammatory in character. The liver showed evidence of terminal hematogenous generalization of the tuberculosis, there being small proliferative tubercles scattered through the section. Sections of the recurrent laryngeal nerve, using trichrome, Loyez, neuroglia, and Sudan IV stains, showed no inflammatory or degenerative changes.

DISCUSSION

In our previous review of the literature on sarcoma of the lung we referred to the well known fact that the histological appearances of inflammatory lesions and overgrowths of reparative tissue may simulate round and spindle cell sarcomata. With this in mind we reviewed the sections of the two bronchoscopic biopsies and of the material coughed up following the first bronchoscopy, and found no evidence pointing to such an etiology, all the sections showing spindle cell sarcoma with no subjacent or adjacent foci of tuberculosis. There remains the remote possibility that there was a tuberculous focus in adjacent pulmonary parenchyma or in one of the peribronchial lymph nodes responsible for the abnormal overgrowth of fibrous tissue. That this is extremely unlikely is attested by the lack of any similar microscopic findings reported in the literature. The usual finding in the event that an active tuberculous focus encroaches on a bronchus consists at first of a non-specific, later of a specific inflammatory

reaction in the bronchial wall, neither of which obtained here. It may be concluded, therefore, that the neoplastic process was not derived from a tuberculous focus, either in the adjacent pulmonary parenchyma, bronchus, or lymph node.

We may then assume that this is a true case of spindle cell sarcoma, arising probably in the bronchial submucosa, and apparently cured by deep roentgen therapy. That radiation reached the area of the neoplasm is evidenced by the "postradiation" calcific changes in the walls of adjacent vessels. The only remaining evidence of a previously existing growth was the fibromatous nodule at the site of the former tumor.

The part played in this case by tuberculosis can be reconstructed on the basis of known pathological changes, and probable pathogenesis. The cavity, which was first noted on the final admission, was probably an uncomplicated tuberculous lesion. The assumption that it was an abscess, secondary to bronchial obstruction, and that the abscess in turn eroded a tuberculous focus, is unlikely, since there was no evidence of bronchial obstruction either at bronchoscopy or at postmortem examination. Furthermore, until the last week, the sputum did not show the foulness usually associated with this type of abscess. The autopsy did reveal, however, a tuberculous endobronchitis throughout the bronchi leading to the cavity, suggesting that the inflammatory disease of the bronchi was secondary to parenchymal tuberculosis.

The terminal gangrene of the right upper lobe was most probably due to thrombosis of the upper lobe branch of the right pulmonary artery, and the fetidity of the sputum resulted from subsequent infection of the open cavity with anaerobic organisms. This mechanism is well recognized as accounting for occasional cases of putrid infection of a preexisting tuberculous cavity.

In order to explain the rapidly progressive tuberculosis we are inclined to suspect that the necessarily heavy dosage of roentgen-rays played a part. It is known that the activity of exudative tuberculous lesions is increased, and that caseation is accelerated by roentgen therapy. In this case, before accelerating caseation of the active lesion, irradiation may have either activated a quiescent tuberculous focus, or rendered the pulmonary parenchyma more vulnerable to tuberculous infection.

We are unable to explain the recurrent laryngeal nerve palsy, which was noted independently by two observers.

SUMMARY

We have presented a case of spindle cell sarcoma of the bronchus, treated and apparently cured by intensive deep roentgen therapy, in which death supervened as a result of rapidly progressive pulmonary tuberculosis, complicated terminally by pulmonary gangrene due to thrombosis of the pulmonary artery.

We wish to express our gratitude to Drs. John H. Richards, J. Burns Amberson, Jr., and Douglas Symmers for suggestions and criticisms aiding the preparation of this report.

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EDITORIAL

THE RÔLE OF MONONUCLEAR PHAGOCYTES IN IMMUNITY TO TUBERCULOSIS

IMMUNITY to tuberculous infection differs in many ways from that occurring in infections with most of the ordinary pathogenic bacteria. In the laboratory animals which have been most carefully studied and probably in man any notable degree of resistance seems to depend upon the presence of living tubercle bacilli in the body tissues. If a normal rabbit or guinea pig is inoculated locally with a suitable dose of a pathogenic strain, the animals show but little resistance to the infection, the organisms multiply freely and the infection becomes disseminated. If, however, such an injection is made into an animal previously infected, a marked inflammatory reaction promptly occurs in the tissues about the site of injection, which tends to prevent multiplication of the bacilli and to restrict their spread.

The mechanism by which this immunity to reinfection is brought about has not been entirely elucidated. Attempts to demonstrate significant activity in the serum of such animals have failed for the most part. Antibodies in relatively low titer have been demonstrated, but such sera do not show direct bactericidal activity *in vitro*, and they have not shown appreciable protective or curative power. It has therefore been believed that an altered activity of the tissue cells must play an essential part in the process. Extensive histological and cytological studies have indicated that the mononuclear phagocytes are largely concerned in the defense reaction.

In earlier experiments Lurie¹ demonstrated that the inoculation of immune (that is, previously infected) animals results in a much more marked and prompt mobilization of mononuclear phagocytes than occurs in a normal animal. Mononuclear phagocytes obtained from immune animals by intraperitoneal injections of sterile irritants like aleuronat showed a greater capacity to phagocytize tubercle bacilli *in vitro* than did those from normal animals, regardless of whether normal serum or immune serum was added to the mixture. However, they also showed an increased capacity to take up carbon particles and staphylococci, a phenomenon which can not be ascribed to a specific immune reaction. Furthermore, these "immune" cells showed some morphological differences from those of normal animals. They were often larger, contained more abundant cytoplasm, more numerous and larger vacuoles stainable by neutral red in supravital preparations and larger pseudopodia, and cells showing mitotic or amitotic division were more numerous. A similar increased outpouring of phagocytes in the tuberculous animal was observed also after injections of nonspecific irritants.

¹ LURIE, M. B. Studies on the mechanism of immunity in tuberculosis. The mobilization of mononuclear phagocytes in normal and immunized animals and their relative capacities for division and phagocytosis, *Jr Exper Med*, 1939, **111**, 579-605.

Such observations suggested a heightened physiological activity on the part of the sensitized animal rather than a manifestation of specific immunity. However, the tubercle bacilli failed to multiply in phagocytes from immune animals, whereas they did so actively in cells of normal animals.

Attempts to determine the parts played by serum antibodies, on the one hand, and by tissue changes, on the other, in this inhibition of growth heretofore have not led to conclusive results. In tissue cultures *in vitro*, mononuclear phagocytes from immune animals have shown no greater inhibitory effect upon the multiplication of tubercle bacilli than those from normal animals.² Manifestly, however, it is difficult in tissue cultures to maintain conditions comparable to those in the animal body for a considerable period of time, and such negative results could not be regarded as conclusive.

In recent ingenious experiments Lurie³ has furnished new and more direct proof of the rôle played by these cells in the defense process. He utilized the anterior chamber of the eye of albino rabbits as a culture medium for the phagocytes, inoculating into one eye, for example, cells from an immune animal, and into the other eye, cells from a normal animal as a control.

He first obtained monocytes which had taken up tubercle bacilli *in vivo*, by injecting normal and immune rabbits subcutaneously with a virulent culture. Two days later he excised the regional lymph nodes and cut them into small fragments which were washed in sterile Tyrode's solution and injected into the anterior chamber of the eyes of a normal rabbit. He also used suspensions of bone marrow from both normal and immune animals which had previously received intravenous injections of tubercle bacilli. After about 14 days the animals were killed and the eyes examined. By histological and cultural studies he demonstrated that the number of living tubercle bacilli in the cells from the normal animal was much greater than in the cells from the immune animal, although the "immune" cells at the time of the inoculation had phagocyted more bacilli than the normal cells. The cells of the immune animal, therefore, markedly inhibited the growth of the tubercle bacilli which they had ingested, as compared with the multiplication of the bacilli in the normal cells. This experiment, however, did not determine whether this activity depended upon a change inherent in the cell itself, or whether it was due to the action of the serum of the immune animal upon the bacilli before their ingestion.

To determine this point, Lurie obtained suspensions of mononuclear phagocytes from both normal and immune rabbits by making intrapleural injections of gum acacia solution. The cells in the resulting exudates were washed to free them as thoroughly as possible of body fluids, and similar suspensions were prepared in citrated salt solution. To such suspensions were

² Rich, A. R., and McCulloch, H. A. Enquiry concerning role of allergy, immunity and other factors of importance in pathogenesis of human tuberculosis, *Bull. Johns Hopkins Hosp.* 1929, xlv, 273-422.

³ Lurie, M. B. Studies on the mechanism of the immunity in tuberculosis. The rate of tubercle bacilli ingested by mononuclear phagocytes derived from normal and immunized animals. *Jr. Exper. Med.*, 1942, lxxv, 247-278.

added serum, either from a normal or an immune animal, as required by the experiment, and a suitable suspension of living virulent tubercle bacilli. After a preliminary incubation to permit phagocytosis to take place the supernatant fluid was removed by brief centrifugalization to get rid of the free bacilli, and replaced by the same type of serum originally present in the mixture. A portion was then inoculated into the anterior chamber of the eye of a normal rabbit, and after two to three weeks the eyes were examined as in the previous experiment.

In this way Lurie compared first, the fate of tubercle bacilli when phagocytized by normal cells in the presence of normal serum, with that when immune serum was used, second, the activity of cells from a normal animal with that of cells from an immune animal when both were suspended in normal serum, and third, when both were suspended in immune serum. The results as described were clear cut. Cells from an immune animal regularly inhibited the growth of the ingested tubercle bacilli, regardless of whether they were suspended in normal serum or in immune serum. On the other hand, under the conditions of the experiment, immune serum did not impart any constant or significant inhibitory activity to normal phagocytes.

These experiments do not exclude the possibility that serum antibodies may contribute to the body's defense from tuberculosis. It is probable that they do so. Earlier experiments of the same investigator¹ showed that if tubercle bacilli were placed in bags impregnated with collodion into which phagocytes could not penetrate, and if the bag was implanted into the peritoneal cavity of a tuberculous animal, multiplication of the organisms was inhibited. When implanted into a normal animal, however, extensive multiplication took place.

The work does demonstrate, however, that the resistance of a tuberculous animal to reinfection depends upon an increased capacity of the phagocytes to destroy or inhibit the growth of the organisms. This change appears to be inherent in the cell itself, and it does not depend upon the presence of immune bodies in the serum or upon the organ environment in which the cells grow.

¹ LURIE, M. B. Studies on the mechanism of the immunity in tuberculosis. The role of extracellular factors and local immunity in the fixation and inhibition of growth of tubercle bacilli, *Jr. Exper. Med.*, 1939, **114**, 555-578.

REVIEWS

Clinical Hematology By MAXWELL M WINTROBE, M D , Ph D 792 pages,
24 × 15 cm Lea & Febiger, Philadelphia 1942 Price, \$10 00

This volume represents an excellent contribution to the field of hematology. Written by an eminent authority on the subject, the material is covered in an authoritative and lucid manner. Fundamental data concerning the constituents of the blood are fully presented. The blood dyscrasias as well as certain tumor-like conditions involving the blood-forming organs are thoroughly covered. The subject matter is completely documented as evidenced by a bibliography of some twenty-four hundred references many of which are current. Throughout the book discussions of hematological technics are incorporated in chapters of which they logically form a part. Selection of technics has usually been done on the basis of the personal experience of the author. In the main the technics are well chosen. The illustrations, graphs, and charts are of uniformly high quality. This volume can be unreservedly recommended to all persons interested in hematology.

M S S

The Treatment of Burns By A B WALLACE, M B , F R C S Ed , M Sc (McGill)
113 pages, 17 × 11 cm Oxford University Press, New York City 1941
Price, \$1 50

This publication, one of the Oxford War Manuals, is a comprehensive and simply written work, but the reviewer feels that its style may convey to the reader an underestimation of the extent of care that burns require.

The author stresses the absolute importance of shock therapy first, reviews fully the varied types of local treatments, and presses the issue of early skin grafting. These comprise, in essence, the major points in the handling of such patients, particularly in war. However, two important points which should be stressed are that under no circumstances should a general anesthetic be given to a burn patient in shock and that, in the main, most cases can be cleaned gently and thoroughly without anesthesia. Dr. Wallace also stresses extraneous heat in shock, this, however, should be used with extreme discretion so as not to break down nature's protective vasoconstrictor mechanism. These facts are important even in the streamlined treatments of wartime.

Lastly, Dr. Wallace's portrayal of "acute toxemia" is very poor and is not at all in agreement with the concepts of liver insufficiency or hepatorenal syndrome cited in the literature on burns or as exemplified by burns of 50 per cent or more as seen by the reviewer.

Nevertheless, this book should serve as a refresher text and should acquaint the novice with the intricate problem of burns.

C M R

The Physiology of the Kidney By HOWLER W SMITH, A B , Sc D , M S (Hon)
310 pages, 22.5 × 15 cm Oxford University Press, New York City 1937
Price, \$1 50

This book is an adequate, detailed treatise on the physiology of the kidney. The author has been most thorough and complete in his discussion of a rather complex and lengthy subject.

The book is logically arranged with a discussion of the anatomy of the kidney and the theories of renal function in the first chapters. The portion of the book devoted to the renal clearance of inulin, phenol red, and similar subjects is most adequate, and is enhanced by generous reference to the original works. This

subjects are brought up to date, and should prove of value to those interested in this topic

The book is too detailed to be of practical value to the clinician, but will be a real asset to the student of physiology, and particularly those interested in physiological research and its allied fields

W K D

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them

Standard Nomenclature of Disease and Standard Nomenclature of Operations Edited by EDWIN P JORDAN, M D 1022 pages, 19.5 × 12.5 cm 1942 American Medical Association, Chicago

Nutrition and the War Second Edition By GEOFFREY BOURNE, D Sc 148 pages, 19 × 13 cm 1942 The Macmillan Company, New York Price, \$1.50

Central Autonomic Regulations in Health and Disease By HEYMEN R MILLER, M D Introduction by JOHN F FULTON, M D 430 pages, 23.5 × 16 cm 1942 Grune and Stratton, Inc, New York Price, \$5.50

Starling's Principles of Human Physiology Eighth Edition Edited and revised by C LOVATT EVANS, D Sc, F R C P, F R S, LL D (B'ham) Chapters on the Special Senses revised by H HARTRIDGE, M A, M D, Sc D, F R S 1247 pages, 24.5 × 16 cm 1942 Lea and Febiger, Philadelphia Price, \$10.00

War Medicine—A Symposium Editor WINFIELD SCOTT PUGH, M D, Commander (M C) U S N retired Associate Editor EDWARD PODOLSKY, M D Technical Editor DAGOBERT D RUNES, Ph G 525 pages, 23.5 × 15.5 cm 1942 Philosophical Library, Inc, New York Price, \$7.50

Psychotherapy in Medical Practice By MAURICE LEVINE, M D 320 pages, 22 × 15 cm 1942 The Macmillan Company, New York Price, \$3.50

Advances in Internal Medicine Vol 1 Editor J MURRAY STEELE, M D 292 pages, 23.5 × 15.5 cm 1942 Interscience Publishers, Inc, New York Price, \$4.50

Emergency Care By MARIE A WOODERS, B S, R N, and DONALD A CURTIS, M D 560 pages, 22.5 × 15.5 cm 1942 F A Davis Co, Philadelphia Price, \$3.50

Synopsis of Pathology By W A D ANDERSON, M A, M D 661 pages, 20 × 13 cm 1942 C V Mosby Co, St Louis Price, \$6.00

Shock Its Dynamics, Occurrence and Management By VIRGIL H MOON, A B, M Sc, M D 324 pages, 24 × 15.5 cm 1942 Lea and Febiger, Philadelphia Price, \$4.50

JOURNAL

Clinics, June 1942 issue, Vol I, No 1 Edited by GEORGE MORRIS PIERSOL, M D 264 pages, 23 × 15.5 cm Published bimonthly by J B Lippincott Co, Philadelphia Price, \$12.00 per year

COLLEGE NEWS NOTES

SUPPLEMENTARY LIST OF MEMBERS OF THE COLLEGE ON ACTIVE MILITARY DUTY

In the July and September, 1942, issues of this journal there appeared a list of the Fellows and Associates of the American College of Physicians who were on active duty with the armed forces of their country. Since the publication of these lists the following members of the College have also been reported on active duty

Frank M Adams
Harry A Alexander

Gerald S Backenstoe
Fred E Ball, Jr
Joseph C Bell
Murray Benson
L Minor Blackford
J Lewis Blanton
James L Borland
Clarence H Boswell
Burdette J Buck
Aaron L Burger
Paul A Burgeson
William C Buschemeyer
M Paul Byerly

Eric M Chew
T Sterling Claiborne
Hunt Cleveland
Henry L Cooper
Linn F Cooper
Erle B Craven, Jr

William M Donovan
Edgar Durlin

Clarence W Erickson
A Carlton Ernstene
George F Evans

James O Finney
Russell A Flack
Harry J Foley, II
Carl H Fortune
Saverio C Franco
Paul K French
Richard D Friedlander

Clarence I Gardner, Jr
Lee P Gay
Wilbur R Gibson

Robert W Gordon
J Richard Gott, Jr

Henry H Haft
Ian B Hamilton
Paul V Hamilton
J Fletcher Hanson
Seale Harris, Jr
Francis J Heringhaus
Frederick K Herpel
Howard E Heyer
Charles S Higley
Donald A Hirsch
J Morris Horn
Arthur T Hurst

Donald W Ingham

Clyde R Jensen
Alf C Johnson
Allen S Johnson

Harry M Kandel
William K Keller
Archibald D Kennedy
Russell W Kerr
Boyd G King
Jack D Kirshbaum
Elmer E Kottke

Louis H Landay
Herman A Lawson
Howard J Lee
Howard P Lewis
Joe H Little

H Four Machlan
Lorenzo D Massey
Fred Mathers
Arthur C McCarty
Richard F McLaughlin
James Byron McMaster

Samuel Millman
Flavius D Mohle
Robert G Murphy

Robert J Needles
John Noll, Jr
F Garm Norbury
Thomas O Nuzum

Kenneth A Owen

Hubert M Parker
Theodore J Pfeffer

Warren W Quillian

Richard Reeser, Jr
Donald H Root
Bernard D Rosenak
Louis Rosenbaum
E Driver Rowland

Sloan G Stewart
Merritt H Stiles
Arthur G Sullivan
Frederick C Swartz

William G Talmage
R Henry Temple
David S Traub
William H Trimble

Thomas V Urmey

Theodore R Van Dellen
Walter L Voegtlin

Joe E Walker
Oliver W Welch
William G Weston
Edward E Woldman
Richard H Wood
Irving S Wright

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members

Books

- Dr Blair Holcomb, F A C P, Portland, Ore — "A Diebetic Notebook for Use of the Patient",
Dr J Arthur Myers, F A C P, Minneapolis, Minn — "Man's Greatest Victory Over Tuberculosis",
Dr Lee Douglas van Antwerp, F A C P, Meriden, Conn — "The History of Alpha Kappa Kappa "

Reprints

- Dr Morris M Banowitch, F A C P, Brooklyn, N Y — 2 reprints,
Dr Maurice C Barnes (Associate), Waco, Tex — 4 reprints,
Dr Archibald A Barron, F A C P, Charlotte, N C — 1 reprint,
Dr Clough Turrill Burnett, F A C P, Denver, Colo — 2 reprints,
William E Costolow, F A C P, Commander, (MC), U S Navy — 2 reprints
Dr Ralph L Drake, F A C P, Wichita, Kan — 1 reprint,
Dr Reginald Campbell Edson (Associate), West Hartford, Conn — 1 reprint
Dr Robert H Flinn (Associate), Bethesda, Md — 1 reprint,
Dr Aaron Arnold Karan (Associate), Brooklyn, N Y — 1 reprint,
Dr Howard T Karsner, F A C P, Cleveland, Ohio — 6 reprints
Dr Bert F Keltz, F A C P, Oklahoma City, Okla — 1 reprint,
R Bruce Logue (Associate), Lieutenant, (MC), U S Army — 1 reprint
Horace P Marvin, F A C P, Lieutenant Colonel, (MC), U S Army — 1 reprint
Samuel Millman (Associate), Major, (MC), U S Army — 2 reprints
Dr Aaron E Parsonnet, F A C P, Newark, N J — 4 reprints,

Dr F B Peck, F A C P , Indianapolis, Ind —7 reprints,
 Dr C P Rhoads, F A C P , New York, N Y —1 reprint,
 Dr Louis H Sigler, F A C P , Brooklyn, N Y —1 reprint,
 Pat A Tuckwiller, F A C P , Major, (MC), U S Army—1 reprint

At the annual meeting of the American College of Chest Physicians, held in Atlantic City, N J , June 6-8, 1942, Dr J Winthrop Peabody, F A C P , Washington, D C , was inducted into the Presidency and Dr J Arthur Myers, F A C P , Minneapolis, Minn , was named President-Elect Other officers elected at this meeting were Dr George G Ornstein, F A C P , New York, N Y , First Vice President, and Dr Joseph C Placak, F A C P , Cleveland, Ohio, Chairman of the Board of Regents Shelley U Marietta, F A C P , Brigadier General, (MC), U S Army, was elected Governor for the U S Army Medical Corps and Robert E Duncan, F A C P , Commander, (MC), U S Navy, was elected Governor for the U S Navy Medical Corps

Dr Salvatore Lojacono, F A C P , Jackson, Mich , was recently elected President of the Michigan Trudeau Society

Dr John C White, F A C P , New Britain, Conn , retired from the private practice of internal medicine and became the Medical Director of the New Britain General Hospital on September 1, 1942

At a joint meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia, September 23, 1942, Dr Mahlon Ashford, F A C P , New York, N Y , spoke on "Coordination of Medical Society Activities" Dr Louis H Clerf, F A C P , Philadelphia, addressed the meeting as the retiring President

Dr Julius H Hess, F A C P , Chicago, Ill , was recently appointed a member of the Committee on Youth and Welfare of the Illinois State Council of Defense by the Governor of Illinois

On July 2, 1942, Dr Anton J Carlson, F A C P , Chicago, Ill , gave a Mayo Foundation Lecture in Rochester, Minn , on "The Newer Knowledge of Nutrition—How Much of It Is Knowledge?"

Dr Frank C Hodges, F A C P , Huntington, W Va , was recently named President-Elect of the Ohio Society of Pathologists

Dr Horace B Anderson, F A C P , Johnstown, Pa , spoke on "Plasma Banks" at a meeting of the Eleventh Councilor District of the Medical Society of Pennsylvania in Somerset, July 16 At this meeting Dr Walter F Donaldson, F A C P , Pittsburgh, Secretary of the Medical Society of the State of Pennsylvania, presented a fifty year testimonial certificate to Dr Harry J Bell, F A C P , Dawson

The 101st Annual Meeting of the State Medical Society of Wisconsin was held in Milwaukee, September 14-16 Among the speakers were

- Dr Arlie R Barnes, F A C P , Rochester, Minn —"Diagnosis of Pathologic Conditions of the Heart",
Dr Wesley W Spink, F A C P , Minneapolis, Minn —"The Clinical Applications and Complications of the Sulfonamides",
Dr Edgar A Hines, Jr , F A C P , Rochester, Minn —"Normal Range and Hereditary Factors in Hypertension",
Dr Edward H Rynearson, F A C P , Rochester, Minn —"Actual Clinical Disturbances of the Endocrine Glands",
Dr Tom D Spies, F A C P , Cincinnati, Ohio—"Advances in Vitamin Therapy "
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Dr George Morris Piersol, F A C P , Philadelphia, Pa , has been named Editor of "Clinics," a new bimonthly journal published by the J B Lippincott Company

Dr Walter S Thomas, F A C P , Rochester, N Y , was named President-Elect of the American Society of Clinical Pathologists at its annual meeting in Philadelphia during June

Dr Byrl R Kirklin, F A C P , Rochester, Minn , has been elected President of the American College of Radiology

Dr William C Menninger, F A C P , and Dr Floyd C Taggart (Associate) were recently elected members of the Topeka (Kan) Board of Health

Dr Frank H Krusen, F A C P , Rochester, Minn , discussed physical therapy at a meeting of the Golden-Belt Medical Society in Manhattan, Kan , July 9

Dr Henry H Turner, F A C P , Oklahoma City, Okla , has been reelected Secretary of the Association for the Study of Internal Secretions

Sanford W French, F A C P , Colonel, (MC), U S Army, spoke on "Medical Care of the Soldiers" and Dr James E Paullin, F A C P , President of the College, Atlanta, Ga , spoke on "Medical Care of the Civilian Population in War" at a public lecture sponsored by the Fulton County (Ga) Medical Society

Dr J Harry Murphy (Associate), Omaha, Nebr , spoke on "Diagnosis and Treatment of Tuberculosis in Childhood" at a meeting of the Lee County (Iowa) Medical Society in Keokuk, June 24

Dr Stanley P Reimann, F A C P , Philadelphia, Pa , Chairman of the Cancer Commission of the Medical Society of the State of Pennsylvania, spoke on "Use of a Correlating Subject in Science Teaching" at a meeting arranged for high school science teachers by the Philadelphia Cancer Council

The American Congress of Physical Therapy held its annual session in Pittsburgh, Pa , September 9-12, 1942 Among the speakers were

Dr Ralph Pemberton, F A C P , Philadelphia, Pa —"Refinements in the Treatment of Arthritics Including Physical Therapy",
Christopher J McLoughlin (Associate), Captain, (MC), U S Army—"Physical Therapy in Relation to Military Medicine "

Dr John A Toomey, F A C P , Cleveland, Ohio, conducted a symposium on "Poliomyelitis "

The Idaho State Medical Association held its annual session in Sun Valley, September 17-19, 1942 Among those who participated were

Dr Frank R Menne, F A C P , Portland, Ore —"Pathology of Lymph Nodes," "Pathology of the Prostate Gland," and "Pathology of Cancer of the Stomach",
Dr Edwin E Osgood, F A C P , Portland, Ore —"Principles of Chemotherapy," "Differential Diagnosis of Coma," and "Therapeutic Thinking "

On September 1, 1942, Dr Hugh A McGuigan, F A C P , retired as Professor of Pharmacology and Therapeutics at the University of Illinois College of Medicine, Chicago

Dr Arthur U Desjardins, F A C P , Rochester, Minn , spoke on "A Group of Persons Whose Skin and Subcutaneous Tissues are Usually Sensitive to Roentgen Rays" at the annual meeting of the American Roentgen Ray Society in Chicago, Ill , September 15-18, 1942

The Mississippi Valley Trudeau Society and the Mississippi Valley Conference on Tuberculosis held their annual sessions in Chicago, Ill , September 16-18, 1942 Among the speakers at a joint session, September 17, were

Dr Oscar A Sander, F A C P , Milwaukee, Wis —"Surveying Industrial Personnel",
Dr Oscar Lotz, F A C P , Milwaukee, Wis —"The Tuberculin Test and Tuberculosis Control",

Dr J Arthur Myers, F A C P , Minneapolis, Minn —"County Accreditation for Tuberculosis Control"

Dr James H Styg II, F A C P , Indianapolis, Ind.—"Reinfection Tuberculosis in Younger Children "

Dr Horton C Hinshaw, F A C P , Rochester, Minn , spoke on "Effect of Reduced Barometric Pressure on Pneumothorax" at a meeting of the Trudeau Society, September 18

The Wyoming State Medical Society held its 39th Annual Meeting in Cheyenne, August 16-18, 1942 Among the speakers were

Dr Thomas D Cunningham, F A C P , Denver, Colo —"Virus Pneumonias (So-Called)",
 Dr George E Baker, F A C P , Casper, Wyo —"Rocky Mountain Spotted Fever "

The Omaha Mid-West Clinical Society will hold its 10th Annual Assembly in Omaha, Nebr , October 26-30, 1942 One of the sessions of this meeting will be devoted to a symposium on "Newer Concepts Regarding Hypertension and Its Treatment " Among the guest physicians who will speak at this Assembly are

Dr Elmer L Sevringhaus, F A C P , Madison, Wis ,
 Dr Russell L Haden, F A C P , Cleveland, Ohio,
 Dr Herman H Riecker, F A C P , Ann Arbor, Mich ,
 Dr Francis E Senear, F A C P , Chicago, Ill ,
 Dr Irvine H Page (Associate), Indianapolis, Ind

PEPTIC ULCER FILM AVAILABLE

There is now available for free showings before groups of physicians the first complete movie film on peptic ulcer, in color and with sound track

The film is entitled "Peptic Ulcer" and was produced under the direction of the Department of Gastro-enterology of the Lahey Clinic of Boston The American College of Surgeons has awarded its seal of approval to the film

Running time of the film is 45 minutes, 1600 feet of 16 mm film, and covers a presentation of the following problems of peptic ulcer Pathogenesis, diagnosis, treatment, pathology, complications, including obstruction, hemorrhage, and perforation, gastric ulcer, surgery and jejunal ulcer

Arrangements for a showing of the film may be made by writing to the Professional Service Department of John Wyeth and Brother, Inc , Philadelphia, who will provide projection equipment, screen, film, and operator for medical groups, without charge

The 15th Annual Graduate Fortnight of the New York Academy of Medicine will be held October 12-23, 1942 The subject of this Fortnight will be "Disorders of the Nervous System " The program will include morning panel discussions, afternoon hospital clinics, evening addresses, and scientific exhibits and demonstrations Among the Fellows of the College who will speak at the evening sessions are

Dr Edward A Strecker, F A C P , Philadelphia, Pa —"Military Psychiatry "
 Dr Harold G Wolff, F A C P , New York, N Y —"The Emotions and Disease",
 Dr Walter Freeman, F A C P , Washington, D C —"Prefrontal Lobotomy "

Dr C C Burlingame, F A C P , Hartford, Conn , and Forrest M Harrison, F A C P , Commander, (MC), U S Navy, will participate in a panel discussion on

"Psychoneuroses of War" Thomas T Mackie, F A C P, Lieutenant Colonel, (MC), U S Army, and Dr Norman Jolliffe, F A C P, New York, N Y, will participate in a panel discussion on "The Vitamins in Disorders of the Nervous System" Dr Harold G Wolff, F A C P, New York, N Y, will participate in a panel on "Psychotherapy"

Dr Arthur F Chace, F A C P, is Chairman of the Committee on Medical Education of the New York Academy of Medicine, Dr F Warner Bishop, F A C P, Chairman of the Committee on Hospital Clinics, Dr Charles F Tenney, F A C P, Chairman of the Committee on Panel Discussions, and Dr Mahlon Ashford, F A C P, is Secretary

DR ELLSWORTH L AMIDON ELECTED ACTING GOVERNOR FOR VERMONT

Dr Paul K French, F A C P, College Governor for Vermont, has entered upon active military service as Major in the U S Army Medical Corps Dr Ellsworth L Amidon, F A C P, of Burlington, has been elected by the Executive Committee of the Board of Regents as Acting Governor to serve during Major French's absence Dr Amidon is Associate Professor of Medicine at the University of Vermont College of Medicine and Medical Director of the Mary Fletcher Hospital He is a Diplomate of the American Board of Internal Medicine

The resignation of Dr Ray M Balyeat, Oklahoma City, Okla, as a Fellow of the American College of Physicians was accepted by the Board of Regents at St Paul on April 21, 1942

Dr Barnett Greenhouse, F A C P, New Haven, Conn, spoke at the New Haven Medical Association on June 17, 1942 His subject was "Clinical Manifestations of Pyruvic Acid Metabolism I The Use of B₁ in Uncontrolled Diabetes II The Use of B₁ in Protamine Insulin Treated Cases Manifesting Hypoglycemic-like Symptoms at Elevated Blood Sugar Levels"

REGIONAL MEETING OF COLLEGE MEMBERS IN WEST VIRGINIA

On July 14, 1942, the Fellows and Associates of the College in West Virginia held a regional meeting at Huntington under the Governorship of Dr Albert H. Hoge, F A C P, Bluefield

Dr Bayard F Horton F A C P, Rochester, Minn, who was the guest of honor, gave a most interesting discussion on the heat control of the human body and on the various experiments that have been conducted in his laboratory at the Mayo Clinic

There was also a general discussion by the West Virginia members of the program of the St Paul Session of the College This discussion included a detailed report on the action of the Board of Regents concerning the waiver of College dues for members of the College called to active duty with the armed forces of their country This action of the Board of Regents was very popular and well received

SPECIAL NOTICES

EXECUTIVE OFFICE OF THE PRESIDENT
NATIONAL RESOURCES PLANNING BOARD
THE SCIENCE COMMITTEE

MEETINGS OF SCIENTIFIC AND LEARNED SOCIETIES

Numerous inquiries are being received from the officers of scientific and learned societies with respect to the possibility or desirability of holding their annual meetings. The Science Committee (advisory to the National Resources Planning Board) which is composed of members designated by the four councils (National Research Council, American Council on Education, American Council of Learned Societies, Social Science Research Council) has thought it desirable to issue the following statement, which has been prepared after consultation with the branches of the Federal Government most concerned. This statement should not, however, be considered an official statement on the part of any branch of the Federal Government.

In view of the fact that the present emergency calls for the greatest mobilization of scientists, scholars, and educators in the history of the United States, it is clear that the societies and associations into which they are organized have an important part in the war effort. This part includes not only direct participation by scientists, technologists, scholars, and others in war activities, but also the discussion of present and future problems and the maintenance of a vigorous intellectual life. There are no fields of knowledge which are not affected, and which have not some contribution to make.

It may safely be assumed, therefore, that the meetings of scientific, scholarly, and educational societies and associations may be so organized as to be in the public interest. It is important, however, that these meetings should be organized in such a way as not to interfere in any way with the actual prosecution of the war.

The Science Committee suggests, therefore, that each society or association should consider the relationship which its field or discipline bears to the war effort, and the contribution that it can make, and that it should plan the program of its meeting with this relation or contribution in view, not overlooking, however, the importance of giving consideration to the post-war period, nor the necessity of maintaining such activities as contribute to a strong national intellectual life.

The Science Committee points out, however, that so far as possible meetings should not be held in or near defense areas, especially the ports and cities of the Atlantic seaboard, and that they should be held on such days of the week as to avoid, as far as possible, week-end (Friday noon to Monday noon) travel. The suggestion is made that some of the large associations may find it advantageous to organize their annual meeting in regional gatherings rather than in a single meeting in one place. It is furthermore suggested that the societies and associations should distribute their meetings among different cities in order to avoid congestion at any one point or along routes of travel.

The Science Committee has been requested to point out the increasing difficulty of handling civilian traffic, the difficulty in securing space and seats, the possibility of late trains and misconnections, and the importance of voluntary curtailment of nonessential travel.

It has further been suggested to the Science Committee that meetings not closely connected with the war effort should be postponed, and that attendance at all meetings should be confined to those whose presence or participation is deemed to be useful. Finally, the Science Committee wishes to point out that the above statement is based upon conditions of transportation that exist at the present time, and

that changes in those conditions may take place and may necessitate radical changes in plans for meetings. Organizers of meetings should accordingly be prepared promptly to make necessary changes in their plans.

EDWIN B. WILSON
Chairman, Science Committee

WASHINGTON, D. C., AUGUST 20, 1942

The Surgeon General of the Army published detailed information concerning policies governing the initial appointment of physicians as medical officers on April 23, 1942. Necessary changes are given wide publicity, at his request, in order that the individual applicants, and all concerned in the procurement of medical officers, may know the status of such appointments.

The current military program provides for a definite number of position vacancies in the different grades. The number of such positions must necessarily determine the promotion of officers already on duty and, in addition, the appointment of new officers from civilian life. Such appointments are limited to qualified physicians required to fill the position vacancies for which no equally well qualified medical officers are available. Such positions calling for an increase in grade should be filled by promotion of those already in the service, insofar as possible, and not by new appointments.

If this policy is not followed, it would definitely penalize a large number of well qualified Lieutenants and Captains already on duty by blocking their promotions which have been earned by hard work. In view of these facts, it has been deemed necessary to raise the standards of training and experience for appointment in grades above that of First Lieutenant.

With this in view, The Surgeon General has announced the following policy which will govern action to be taken on all applications after September 15, 1942.

All appointments will be recommended in the grade of First Lieutenant with the following exceptions:

Captain 1. Eligible applicants between the ages of 37 and 45 will be considered for appointment in the grade of Captain by reason of their age and general unclassified medical training and experience.

2. Below the age of 37 and *above* the age of 32, *consideration* for appointment in the grade of Captain will be given to applicants who meet all of the following minimum requirements:

- a. Graduation from an approved medical school
- b. Internship of not less than one year, preferably of the rotating type
- c. Special training consisting of 3 years' residency in a recognized specialty
- d. An additional period of not less than 2 years of study and/or practice limited to the specialty

3. Eligible applicants who previously held commissions in the grade of Captain in the Medical Corps (Regular Army, National Guard of the United States, or Officers Reserve Corps) *may be considered* for appointment in that grade provided they have not passed the age of 45 years.

Major 1. Eligible applicants between the ages of 37 and 55 *may be considered* for appointment under the following conditions:

- a. Graduation from an approved school
- b. Internship of not less than one year, preferably of the rotating type

- c Special training consisting of 3 years' residency in a recognized specialty
- d An additional period of not less than 7 years of study and/or practice limited to the specialty
- e The existence of appropriate position vacancies
- f Additional training of a special nature of value to the military service, in lieu of the above

2 Applicants previously commissioned as Majors in the Medical Corps (Regular Army, National Guard of the United States, or Officers Reserve Corps) whose training and experience qualify them for appropriate assignments may be *considered* for appointment in the grade of Major provided they have not passed the age of 55

Lieutenant Colonel and Colonel In view of the small number of assignment vacancies for individuals of such grade, and the large number of Reserve Officers of these grades who are being called to duty, such appointments will be limited. Wherever possible, promotion of qualified officers on duty will be utilized to fill the position vacancies.

Much misunderstanding has arisen concerning recognition by Specialty Boards and membership in specialty groups. It will be noted that mention is not made of these in the preceding paragraphs. This is due to the variation in requirements of the different Boards and organizations. Membership and recognition are definite factors in determining the professional background of the individual, but are *not* the deciding factors, as so many physicians have been led to believe.

The action of the Grading Board, established by The Surgeon General in his office, is final in tendering initial appointments. Proper consideration must be given such factors as age, position vacancies, the functions of command, and original assignments. All questionable initial grades are decided by this Board. Due to the lack of time, no reconsideration can be given.

There are in the age group 24-45 more than a sufficient number of eligible, qualified physicians to meet the Medical Department requirements. It is upon this age group that the Congress has imposed a definite obligation of military service through the medium of the Selective Service Act. The physicians in this group are ones needed *now* for active duty. The requirements are immediate and imperative. Applicants beyond 45 years may be considered for appoint only if they possess special qualifications for assignment to positions appropriate to the grade of *major* or above.

The Directing Board of the Procurement and Assignment Service of the War Manpower Commission told its State Chairman for Physicians to retain in their present positions full-time and part-time industrial physicians and physicians serving State industrial hygiene bureaus on a full-time basis.

Chairman Paul V. McNutt, of the War Manpower Commission, through Dr. Frank H. Lahey, chairman of the directing board, said in a statement to the state chairmen:

"A serious situation is developing in some states because physicians under 45 years of age who are essential in their present positions as key men in industrial practice are being declared available by State Chairmen or are being approached directly by recruiting boards with instructions to apply for a commission in the Army Medical Corps.

"The Selective Service System and the Surgeons General of the Army and Navy are cooperating with us to keep at their posts the physicians declared to be essential by our State Committees."

Mr McNutt asked the physicians to be guided by the following criteria, which have been recommended by the Committees on Industrial Health and Medicine and have been approved by the Directing Board

A physician employed in industry is deemed to be essential when the following conditions exist

A Full-time industrial physician

1 The physician is employed by an industry which is manufacturing war materials exclusively or under priority ratings, and

2 The physician gives his full time to the industry or 40 or more hours weekly, has been so employed for at least two years or is especially trained for that purpose and is carrying on an acceptable health maintenance program, and

3 The physician is performing the functions of a medical director or department head or of a specialist or is the only physician employed

4 Assistant physicians who perform routine functions under direction, and are employed on a full-time basis, are deemed essential until they can be replaced within a reasonable time (3 to 6 months)

B Part-time industrial physician

1 The physician serves part-time two or more industries engaged exclusively in the manufacture of war materials or under priority ratings, provided his total part-time service is the equivalent of 40 or more hours weekly Note The physician who serves on call only is not deemed to be essential

C The physician serves a State industrial hygiene bureau on a full-time basis

Chairman Paul V McNutt of the War Manpower Commission announced the standards by which public health physicians should be considered essential to public health interests and non-available for military duty

The Procurement and Assignment Service of the War Manpower Commission adopted the standards upon recommendation of its Advisory Committee on Public Health, headed by Dr Carl Reynolds, State Health Officer for North Carolina

According to the Procurement and Assignment Service standards, "A physician should be considered essential to civilian public health interests and, therefore, not available for military duty provided he comes within either one of the two following categories

- 1 A full-time medical officer in charge of a health service of a governmental unit or administrative district, such as State, district, county, and city
- 2 Full-time heads or chiefs of administrative units within a health department
For example tuberculosis, venereal diseases, maternal hygiene, infant care, epidemiology vital statistics, etc

Methods of health service differ throughout the States, public health problems vary with localities population densities, and in terms of war industries, military centers, and so forth which may create special problems when located," said the report of the Advisory Committee on Public Health to the Directing Board of the Procurement and Assignment Service

"The committee, therefore, does not deem it feasible to submit any specific recommendations for Nation-wide application as to the essentiality of full-time medical officers serving health departments in capacities other than those in the two groups of health above

"In view of these facts, this committee recommends that the essential designation of physicians in capacities other than those described above be determined after conference between the administrative chief of the health department concerned and the State chairman of Procurement and Assignment Service

"Physicians in public health positions, other than those specified in categories 1 and 2, who are under 37 years of age, should expect to be released for military service, except under unusual circumstances, and their places should be taken by older persons

"Special consideration, however, shall be given to trained health officers who have had two or more years of training and service in public health

"Furthermore some of these who may not be essential locally may be needed by the U S Public Health Service for service elsewhere "

Mr McNutt praised the patriotic spirit of those who, when remaining at home, performed their medical services willingly and with the attitude that they were doing their equal share in the present crisis

OBITUARIES

DR ADAH McMAHAN

Dr Adah McMahan, Associate of the American College of Physicians since 1925, of La Fayette, Ind., died June 24, 1942, of postoperative shock following cholecystectomy

Dr McMahan was born January 12, 1869, received her A B degree in 1889 and her A M degree in 1893 from Indiana University. She graduated in medicine from the Northwestern Woman's Medical School, Chicago, in 1897. During World War I, she served in France. She was a former President of the Tippecanoe County Medical Society, a member of the Indiana State Medical Society and of the American Public Health Association, also a Fellow of the American Medical Association. She had formerly served as a member of the Indiana State Board of Health and was on the staff of St Elizabeth and La Fayette Home Hospitals.

Dr McMahan was highly esteemed personally by members of the profession, who also had a high regard for her work.

DR CLARENCE M GRIGSBY

Medicine in the Southwest has lost a staunch and faithful exponent in the passing of Dr Clarence Manning Grigsby, of Dallas, Texas, who died on June 14, 1942, of hypertensive heart disease and angina.

Dr Grigsby was born near Homer, Louisiana, October 27, 1868, and graduated in medicine from the College of Physicians and Surgeons in Baltimore in 1893. He pursued postgraduate studies in all of the medical centers in this country, and served as Associate Professor of Medicine and Professor of Medicine, also as Professor of Clinical Medicine, at Baylor University College of Medicine. At his death he was Emeritus Professor of Medicine at Baylor College.

Dr Grigsby was an ardent supporter of organized medicine, and had served as President of the Dallas County Medical Society and as Chairman of the Sections on Medicine of the Texas State Medical Association and the Southern Medical Association. Many valuable papers were published by Dr Grigsby. He was a Diplomat of the American Board of Internal Medicine, and since 1921 had been a Fellow of the American College of Physicians, serving the College for many years as Governor for Texas. His host of friends in the American College of Physicians will sorely miss Dr Grigsby at the annual meetings, very few of which he ever failed to attend. His ready wit and ever-ready story for all occasions endeared him to everyone who was fortunate enough to know him. His interest in the younger men in the profession has been perpetuated by his will, his entire estate being left to build up the Department of Medical History in Baylor University Medical College, which he served so long and well.

The death of Dr Grigsby will cause deep sorrow to his many friends over the entire country

M D LEVY, M D , F A C P ,
Governor for Texas

DR MAXIMILIAN JOHN HUBENY

Maximilian John Hubeny, F A C P , F A C R , Chicago, born in Leipzig, Germany, October 12, 1880, of Bohemian parentage, died in Chicago, July 2, 1942, aged 61 While enroute in his automobile to the hospital, he was seized with a sudden, severe cardiac attack and, fully realizing its significance, he induced a service station attendant to chauffeur him the remainder of the way They reached the Cook County Hospital, but their arrival was almost coincident with his death, due to an acute coronary occlusion

Heredity endowed him with all the qualifications of a real gentleman, which were augmented by home environment and education To these were subsequently added those of a scholar and scientist By nature he possessed a most amiable disposition and personality, characterized by high ideals and unlimited amount of energy

He received his M D degrees from Hahnemann Medical College and Hospital of Chicago in 1906 and from the College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909 As a medical student he was outstanding, justifying a prediction of success and leadership For a time after graduation, general practice occupied his attention, but very soon he was attracted to roentgenology which was his chosen field during the remainder of his life

At one time Dr Hubeny was Roentgenologist at Hemotin Hospital and at the Municipal Tuberculosis Sanitarium (Chicago), since 1936 he had been Director of the X-Ray Department of Cook County Hospital and Professor of Roentgenology and Chairman of the Department at Cook County Graduate School of Medicine Dr Hubeny was Secretary of the Section on Radiology of the American Medical Association from 1923 to 1926 and at one time was Editor of the journal, "Radiology," and Associate Editor of the "American Journal of Cancer," "The Italian Journal of Radiology," and the "Cuban Journal of Radiology" In 1931 he was awarded a gold medal by the Radiological Society of North America for research Dr Hubeny was a Diplomate of the American Board of Radiology, a member of the American Roentgen Ray Society, a member and past president of the Radiological Society of North America, the Chicago Roentgen Society and the American College of Radiology, a Fellow of the American Medical Association and a Fellow of the American College of Physicians since 1920

His colleagues and friends those who knew him best, cherish his memory as a tried and trusted friend, always kind, sympathetic and most generous to those in need of his assistance Mercenary he was not, for this was

foreign to his nature. He will long be remembered and his passing regretted by all who knew him

FREDERICK TICE, M D , F A C P ,
Chicago, Ill

DR JOSEPHUS PATMAN BOWDOIN

Josephus Patman Bowdoin, Atlanta, Georgia, died on August 7, 1942, at the age of 76. He was stricken at his office and taken to a hospital, where he passed away a few hours later.

Dr Bowdoin was born in Adairsville, Georgia, on May 7, 1866. He attended Atlanta Medical College (now Emory University School of Medicine) and graduated as valedictorian of his class in 1889. Following his graduation, he returned to Adairsville and practiced medicine in Bartow and surrounding counties for nearly 30 years. During this period he served as president of his county medical society, chairman of the district society and surgeon for many years for the N C & St L Railroad.

At the beginning of World War I, Dr Bowdoin volunteered his services and served as a surgeon in the U S Public Health Service. Following this, he entered public health work in Georgia as Director of the Division of Venereal Disease Control, acting in that capacity until July, 1939, and of the Division of Child Hygiene. In 1921 he was elected by the State Board of Health as Deputy Commissioner of Health of Georgia.

In 1920 he began to edit the monthly bulletin, "Georgia's Health" and continued to do so until his death. He contributed many articles to medical journals and was author of "Georgia Baby Book," now in its eighth edition.

Outside of the medical profession, Dr Bowdoin took a large part in fraternal, civic and public affairs, being for many years a member of the Board of Education in Adairsville.

Dr Bowdoin had been a Fellow of the American College of Physicians since 1929.

GLINVILLE GIDDINGS, M D , F A C P ,
Governor for Georgia

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ELECTRO-COMA THERAPY OF PSYCHOSES *

By JOSEPH L. FETTERMAN, M A , M D ,
Cleveland, Ohio

INTRODUCTION

THE therapy of psychoses has advanced rapidly during the past decade. Observation and analysis, hydrotherapy and occupational measures, and symptomatic medication all have their fields of usefulness. However, there have been introduced more specific therapies which depend upon direct chemical and electrical influence upon brain function. In 1932 Sakel¹ developed the insulin shock treatment for schizophrenia, a method which opened a new era in the therapy of psychoses. Shortly thereafter, the use of the metrazol convulsion treatment was the product of the research of von Meduna.² Metrazol, at first recommended for schizophrenia, proved more effective in depressed states. The results of this method were definitely valuable, but the psychologic discomforts and the orthopedic complications were major obstacles in its use. Recently, as an outgrowth of electrical brain study and the accepted use of convulsive therapy, the electro-shock methods were begun in 1938 by Cerletti and Bini.³ Finally, during the last few years, a surgical procedure, frontal lobotomy, was established by the work of Moniz and was introduced into our country by Dr. Walter Freeman.^{4,5}

It is the purpose of this paper to record the clinical results in a series of 70 patients treated by the electrical method. This report includes a tabulation of the therapeutic results in the various types of psychoses and a consideration of the side actions and complications. Also mention will be made of several parallel research studies which have been undertaken. Finally, some interpretation will be offered of the results obtained in the light of the modern concepts of psychoses.

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Thanks are due to Drs. A. T. Steegmann, M. D. Friedman, and S. Baumel, some of whose patients are incorporated in this case study.

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METHOD AND MATERIAL

The technic employed is similar to that which has been outlined by previous writers (Kalinowsky,^{6,7} Gonda,⁸ Impastato and Almansi⁹) The reader may refer to these pioneer papers for a historical review of the subject and for technical details of the apparatus

The method of treatment is briefly as follows Electrodes are placed on the forehead of the patient The apparatus is set at the desired current values This usually means a dose of from 400 to 600 milliamperes at a time interval of from 0.2 to 0.5 second The voltage for such a treatment may range from 60 to 150 volts As the current is applied, unconsciousness occurs instantaneously The patient becomes temporarily rigid in extension or he may flex forward If the dosage has been small, there will be a few muscular twitchings only If the dosage has been adequate, the individual will shake violently in a hard convulsive reaction lasting from 30 to 60 seconds Following the convulsion, there is a period of stupor lasting minutes, from which the patient emerges gradually The return to complete consciousness takes place by stages over a period of from minutes to half an hour or an hour

Each patient receives a course of such treatments, the number of reactions depending upon the individual case As a rule, from 6 to 12 treatments are necessary for a successful result The treatments are given on alternate days, or usually three a week

The material includes a group of private patients who, for the most part, showed evidences of early stages of mental disease These patients were in the psychotic group, most of them had some type of depression and the remainder schizopirenia In considering the therapeutic results, an attempt was made to separate the patients into various diagnostic headings The commonly accepted groups of hebephrenic schizophrenia, paranoid schizophrenia, schizodepressions, simple depressions, agitated depressions, and involutional melancholia were used

It must be pointed out that it is more difficult to classify patients who are in the earlier stages of mental disease than those whose illnesses are far advanced Furthermore, one must realize that classifications are arbitrary and patients are real, and that the modern psychiatrist, using new methods of therapy, cannot accept the former classifications as rigid and final Indeed, the point of view of Singer¹⁰ deserves emphasis He comments upon the difficulty of separating the various diagnostic groups "It is always a problem not of all or none, but of more or less" It is Dr. Singer's thesis that the major symptoms, or the fact of the illness, are produced by the nature and location of the structural damage, whereas the form is determined by the person who is ill Quoting from Singer "Thus, one and the same organic lesion may give rise to a manic-depressive form of psychosis in one person and to a schizophrenic or paranoid psychosis in another" The surprising

results which have been obtained with the electrical method of treatment corroborate the modern point of view of Singer as against the rigid classifications of Kraepelin

TERMINOLOGY

Before mentioning the results obtained, it may be appropriate to present the terms which I have found helpful in discussing this subject. The term "electro-coma therapy" is proposed in place of the phrase "electro-shock treatment." The concept, shock, connotes either a painful and disagreeable electrical sensation or the vasomotor collapse which is part of "surgical shock." In this treatment the patient does not experience any dreadful electrical sensations nor does he show the circulatory collapse which is part of "surgical shock." The essential feature of this method is the period of unconsciousness, although convulsions are also a major feature. The term "electro-coma therapy" is descriptive of the method and does not connote false or unfavorable pictures to the patient and his family.

For the reactions which patients show, the terms "petit" and "grand mal" are used in the current literature. These terms have been introduced because of a certain resemblance to the manifestations of epilepsy. It has been my custom to use the phrase "minor reaction" for a brief episode of unconsciousness without a major convulsion. For the complete reaction with unconsciousness and convulsive state, the term "major reaction" is used. Occasionally the individual will have unconsciousness with marked rigidity and some twitching and shaking movements. For this in-between type of response, the term "moderate reaction" is used. The terms "petit" and "grand mal" have belonged to the concept of epilepsy for ages, likewise, the designation "petit mal" usually applies to a momentary state of hypoco-consciousness and not to complete unconsciousness, which occurs with the electrical method. I have found the designations "minor," "moderate," and "major," as useful, accurate, and free of the epileptic association.

CLINICAL APPRAISAL OF THE THERAPEUTIC VALUE

A detailed summary of the results obtained is included in the accompanying table. This shows the identification of the patient, the age, the duration of symptoms, the number of treatments, and the results obtained. One may summarize the details of the table with the brief statement that the changes resulting from the electro-coma treatment have been remarkable and the percentage of improvement high. Yet this improvement is somewhat selective, more prompt in certain types of patients than in others, and undoubtedly more permanent in certain patients. It may be of value for us to consider the therapeutic benefit from the standpoint of the group of patients treated.

A. The Combined Group of Involutional Melancholia and Agitated Depressions of Later Life. Within these categories are included those patients

whose ages range from 45 to 70 and whose major symptoms are those of depression. The composite picture of a patient in this group is a woman of about 60, previously cheerful, industrious, and capable, who has become sleepless, restless, troubled by visceral distress, and overwhelmed by a sense of catastrophe. Such an individual has been ill for many months, has lost considerable weight, has developed a sense of hopelessness, and has wished for death or has even made suicidal attempts.

The patients in this group respond remarkably well to electro-coma treatment. Eighteen patients belong to this group. All who were treated showed a favorable response. However, in three of the patients there are residual symptoms which indicate that the recovery has not been complete. Several of the patients were close to or above 70 years of age. They had been severely depressed for months. Two of the group had made suicidal attempts. They have shown a surprising recovery, with a return to well-being. Our results in this older age group corroborate the encouraging reports of Robinson,¹¹ who has shown the comparative safety of this method and the good therapeutic response of such patients to the electro-coma treatment:

T V, a woman of 51, was sick for several months in the spring of 1941. She had been a cheerful and capable individual, happy in her home, sociable with friends, and interested in many activities. Gradually she lost the desire for company, could not eat, and became sleepless. Week after week her condition grew worse, she lost a great deal of weight, and was unable to read, eat, or sleep. She was overwhelmed by a sense of hopelessness. After two months of such distress, she attempted suicide by cutting her throat. First aid was given in an emergency hospital and she was then taken to the Post-Shaker Sanitarium. En route to the sanitarium she made another attempt at suicide by jumping out of the car.

She was observed in the hospital for several weeks. She refused all food saying "It doesn't pay to eat, I want only to die. I can't eat, I don't have any bowel movements. My arms and hands are changed, my nerves are twisted in my belly and it seems as though they are moving around like worms. My brain doesn't function any more. There is no use, I am going crazy and no one can help me." These somatic delusions were intense and the patient was agitated with obvious suffering.

The electro-coma treatment was begun early in July. A series of 10 treatments was administered. During the course of the treatment, she became conversational, took an interest in her fellow patients, and remarked "I am anxious to get my nerves collected and to get back to work. I know I am going to be happy." August 1 she stated: "These treatments have helped me a good deal. I know I am going to be well." During the early part of August she was somewhat elated and this cheerful mood continued for a while. The patient was discharged in September and resumed her position in her family. She has been seen several times during the fall of 1941 and has remained symptom free. Indeed, she has gained weight, renewed her usual acquaintance and activities, and is apparently well.

B. Depressions. It is certainly no easy matter to distinguish between endogenous depression and involutional melancholia. We have used the term, endogenous depression, for the cases of younger individuals whose family histories show a strong constitutional tendency to this illness. In several instances these patients have had previous attacks. In the group of

endogenous depressions there were 17 patients. The results in this group of patients have been excellent. Patients who had been ill for months or years responded favorably and quite promptly. As a rule, some six to eight treatments were sufficient. However, after this preliminary course, the patients were observed for a period of several weeks. If there was a tendency to relapse, additional treatments were given. In two instances, an additional course of six treatments was necessary.

A typical case history in this group is that of Mr. W. C.

This patient was 40 years of age, a mechanic by occupation, unmarried, who had been ill for some eight months. A previous attack of depression occurred at the age of 20 and lasted a year and a half.

This individual had been a cheerful, self-confident, and capable person. Gradually he became morose, withdrew from his social contacts, and complained of weakness. The weakness was so profound that he could not work. Gradually the additional features of insomnia, self-accusation, and suicidal thoughts appeared. The patient believed that others were talking about him because of his sinfulness and that in his youth he had developed a habit which had brought about his ruin and from which he could never recover.

A course of six electro-coma treatments was given in a period of two weeks. Like a cloud moving away and revealing sunshine, so there was a remarkable change in this man's mood. The sad face and droopy posture gave way to an effervescent smile and erect, brisk walk. He looked and acted like a happy individual. Treatment was discontinued and he was allowed to go home on trial. Gradually he became sad, inactive, and once more obsessed by dark thoughts. The treatment was resumed and six more electro-coma reactions given. He was discharged in May of 1941 and has remained perfectly well during a period of six months.

C. Schizodepressions. There are many patients who show a definite combination of a markedly depressed mood with hallucinations and delusions, which are usually thought to be characteristic of schizophrenia. One who examines such a patient may be unable to determine whether the illness is a true schizophrenia or a depression. This doubt, when one faces such a patient, substantiates the statement of Dr. Singer which was quoted above. There are obviously individuals who cannot be classified as one or the other but who have an interweaving of mood change and schizophrenic features. The term, schizodepression, is used for such patients. Ten patients are included in this group. The typical patient in this group was a younger individual, often an intelligent and successful personality when well, and often without a family history of psychosis. These patients had active hallucinations and responded directly to them. There were voices which accused the individual of misdeeds or invited the person to some rendezvous. The accusations frequently revolved about the theme of sex. The members of this group did fairly well with electro-coma treatment. Seven have shown a favorable response whereas the improvement in the remaining three has been partial or temporary.

The following case history illustrates this type of patient.

Miss D. N. was a woman of 40, who had been an efficient secretary in a business concern for many years. Gradually the thought occurred to her that she was being

observed by her fellow employees and that one man in particular was sending messages to her. She believed that certain gestures represented messages of love. When she phoned him and he denied any attempts to arrange a rendezvous, she became incensed and then disheartened. She was quite bewildered by this apparent contradiction. Indeed, she not only interpreted the messages, but believed she could hear his voice talking to her. And yet he made a complete denial of any interest in her. She became depressed, could not sleep nor eat, and gave up her work. Saddened and bewildered, she felt there was no way out except death. She made two suicidal attempts. First she cut her wrists, but the bleeding was quickly stopped. Later she injected 360 units of insulin into herself. (She was accustomed to using the insulin syringe in the treatment of her diabetic mother.) After she had injected the insulin there was a change of heart and she immediately injected a concentrated sugar solution to counteract the effect of the insulin.

The patient was taken to the hospital. At first she was negativistic and inaccessible. Later she appeared to be hearing voices and she reported both optical and tactile hallucinations.

The electro-coma treatment was begun in June of 1941. After several treatments the patient became calm. After the ninth treatment, the hallucinations disappeared. The entire course consisted of 12 major reactions.

This patient has been followed (by correspondence) over a period of five months. She has made a splendid recovery, has resumed her place in the home, and is once more an efficient employee of her concern.

D. Manic Psychoses. Two patients, L. R. and L. J., with acute manic psychoses, were treated. Both showed a favorable reduction in the excitement as a result of the electrical treatment. However, in each instance the cessation of treatment was followed by a return of psychomotor restlessness and hypomanic behavior. A second short series of treatments was used, again with a calming influence. Both patients are now well.

E. Schizophrenia. The schizophrenic group undoubtedly encompasses a large assortment of patients. Any study of schizophrenia must differentiate between those individuals who have never achieved full and complete adjustment to life and those who had been successful but then developed serious evidence of illness. The prognosis in the former (dementia precox) is certainly far different from that of the latter.

Three patients with dementia precox were treated. Two of these have improved. However, the improvement is not complete and the prognosis remains unfavorable.

In the larger group of paranoid schizophrenia the list includes 18 patients. Four of these patients have shown little or no improvement. Of these, three were considered advanced cases of schizophrenia. The remaining 14 have shown definite favorable changes as a result of electro-coma treatment. Indeed, practically every patient responded to electricity with an improved attitude and a cheerful mood response. The more serious chronic types of schizophrenia tend to relapse quickly. The others have continued to show progress. One of these patients was truly remarkable in that she had been sick for five years. This patient was treated in the spring of 1941, after several years' previous hospitalization and the failure of metrazol and

insulin shock therapy Since her discharge from the hospital in April, 1941, this patient, F R, has successfully maintained her place in society

Treatment in the schizophrenic group was always begun with a definite attitude of skepticism The malignant nature of schizophrenia is recognized This malignant nature may account for the tendency to relapse after improvement by shock methods The improvement which we have obtained with electro-coma treatment may, like that obtained with insulin, be but a pause in the course of the illness rather than a complete removal of the disease

F Miscellaneous Cases In several instances, the electro-coma method was used for patients who did not belong to the above groups For example, a patient with a severe compulsion neurosis was given a course of eight treatments This was followed by a slight change in behavior, but there was a return of the symptoms when the treatment was stopped A chronic alcoholic, who had periods of depression, was given several treatments The mood change was corrected, but unfortunately the first stop this patient made when he left the hospital was his favorite bar

THE PSYCHOLOGIC SIDE ACTIONS OF ELECTRO-COMA THERAPY

Although the clinical results have been extremely satisfactory, yet certain side actions occur, usually temporary, which are quite disturbing These side actions may be in the form of (1) marked amnesia, (2) periods of elation, and (3) episodes of confusion

1 Amnesia Following an electro-coma treatment, the return to consciousness is gradual, a step by step resumption of mental functions, and it may be a matter of minutes or several hours before the patient is fairly alert Though awake, he is often bewildered, especially because he does not remember what had happened before, during, and immediately after the treatment It is a common experience for a patient to have forgotten the fact that he has received a treatment This amnesia is quite marked as regards the inability to recall time and place The amnesia for events immediately preceding treatment is striking As a rule, there is only a slight and transitory forgetfulness with the first few treatments This amnesia is referred to as lacunar, i.e., a "spotty" memory disturbance With each successive treatment the extent of the forgetfulness may become greater, as though each little spot of amnesia had been pooled into a large lake Thus it is fairly common, particularly in older patients, for considerable blankness to develop after the sixth or eighth treatment Such patients have forgotten how long they have been in the hospital, the names of the people with whom they are in contact, and many of the experiences of the past It is remarkable that many of them have forgotten completely the dreadful, anxious, and suicidal thoughts they had before treatment

There is a tendency toward a spontaneous recovery from such amnesia When the patient is reminded of a certain event he can recall the situation

quite readily and he is apt to remember the episode from this point on. As a rule, patients recover from this memory disturbance in the matter of days or weeks. The longest instance of disturbed memory in this group of patients is that of Mrs. D. P., a woman of 62, who had received eight electrocoma treatments. She improved considerably and was, therefore, allowed to go home within several days following the last treatment. At home she could not remember many of the activities during the month or two before she entered the hospital. But her chief difficulty was that she had forgotten the cooking recipes with which she had been familiar. She was embarrassed when meeting old friends because she could not remember their names or certain social events that she had attended. Mrs. D. P. regained her memory, but it took a matter of some three months before she had fully recovered.

Our observations with regard to amnesia correspond with the favorable prognosis in memory disturbance reported by other workers (Ziskind,¹² Myerson¹³). For example, two of our patients, one a teacher and the other a research assistant, showed marked memory disturbance which lasted for several weeks. Both had made complete recoveries from serious mental illnesses, but were troubled by amnesia. In each case the return of memory was satisfactory. The research worker, whose job it was to translate foreign medical journals, stated that she had regained her normal speed and efficiency in this difficult task.

Some authors have associated the memory disturbances with the change in the brain waves revealed by electroencephalogram. Many observations indicate that there is a brain wave change, marked in the period after the convulsion. These brain waves return to normal in the matter of days or weeks. Hughes and his coworkers¹⁴ state "The longest period after treatment before the electroencephalogram returned to normal was three or four weeks."

2. Elation Frequently, independent of or along with the amnesia, there is a period of elation. This cheery mood is striking, especially when compared with the previous profound depression. The most impressive fact about electrocoma treatment is this frequent change in mood. An individual who had been sad, droopy, and silent may, after several treatments, become active and happy. Occasionally the change does not stop at calmness, poise, and controlled activity. Indeed, some of these patients developed periods of marked overactivity resembling that of a hypomane patient. There are effervescence, loudness, a stream of conversation, and extraordinary sociability. Such elation was shown by Mrs. T. V., whose case history was cited above. For several weeks after the series of electrocoma treatments, this formerly quiet and sad woman became talkative. She would address every patient on the ward, advising him or her to take electrical treatment. She would interrupt their eating, burst between two people who were talking to explain her views in a loud voice. There was a sparkling gleam in her eyes, and her face was wreathed in smiles. She walked about

the ward with a brisk step. She was overconfident of her ability, spoke optimistically of her plans. Gradually, during a period of several weeks the bubbles of effervescence burst and she became more calm. Two months after the treatment was over she had returned to her usual sense of well-being with a normal admixture of confidence and doubt, cheerfulness and sadness. It took about six weeks for the elation to subside.

3 Acute Confusional Episodes A third type of psychologic reaction may be called an acute confusional syndrome. This state is often accompanied by marked amnesia. Patients lose the memory of their previous illness, but are neither calm nor elated. Instead they are tense, excited, hypersensitive to noises, and somewhat in a state of terror. They resemble patients with an acute toxic psychosis. Mrs. E. B. had been depressed for months and a course of treatment was started. After the fourth electrocoma reaction she became restless, sleepless, and developed marked fears. However, she did not discuss these fears openly. Instead, when the doctor approached her, she would pull away somewhat startled. She remained in a state of tension and alarm for 10 days. Such confusional episodes, a combination of bewilderment and terror, were more common in the older group than in the younger patients. Also, this side action was more frequent during the summer than in the spring or fall. Such disturbance is temporary and clears up after some days or weeks. When the confusion disappears, the patients usually return to a normal state. In not a single instance has this confusional period lasted more than several weeks.

COMPLICATIONS OF ELECTRO-COMA THERAPY

A treatment as severe as electrocoma therapy has definite complications. In addition to the psychologic side actions, which are temporary, we must consider certain complications, possibly of a more permanent nature. Let us divide them into (1) immediate reactions and (2) possible later sequelae.

1 Immediate Reactions The immediate complications include chiefly the injuries to the muscular and bony systems. With metrazol there was a fairly high incidence of fractures until patients were kept in hyperextension and restraint. This complication is much less frequent with the electrocoma method. Smith and his group¹⁵ reported that the fracture incidence with the electrical method was one-fourth of that which occurred with metrazol. Furst and Stouffer¹⁶ stated that there were some 3 per cent of fractures of the spine in a series of 115 patients. In our group we have had one bilateral fracture of the mandible and three cases of severe pain in the back. Two of these patients have shown fractures. The instances of fractured spine have occurred recently and for this reason we are planning to use intocostin, as recommended by Bennett.¹⁷

2 Possible Late Sequelae Inasmuch as the electric current traverses the frontal lobes of the brain, one must think of the possible late sequelae of this method. However, Cerletti and Kalinowsky believe that the brain

changes in man are reversible and do not produce serious damage. Further comment on the evaluation of such possible sequelae will be given later.

OTHER STUDIES

Along with the clinical studies reported, several research projects are being conducted. These will be mentioned briefly inasmuch as the papers, when completed, will be published elsewhere.

A. Electrocardiographic Studies Dr Edward Kline took a series of electrocardiographic records before and immediately after treatments in some 40 patients of this group. He has found even less change as a result of the electro-coma method than with metrazol,¹⁸ with which therapy we encountered no significant cardiac disturbances. Although Dr Kline's paper will cover the details, one may mention the fact that several of the patients in this group had known cardiac difficulties. One of the patients, Miss P. O., had once suffered from coronary disease and had been operated on by Dr Claude Beck.¹⁰ Two years later she developed a serious schizodepression which grew steadily worse despite all conservative therapy. As a last resort, after a consultation with Drs Beck, Harold Feil, and O. P. Kimball, the family physician, a course of electro-coma treatment was given. This patient showed no circulatory difficulties as a result of 10 treatments and made a splendid recovery from her mental illness.

B. Anatomic Studies Early this summer, in collaboration with Dr E. Scharrer and Dr D. Bodian, a *Macacus rhesus* monkey, whom we called Miss Darwin, was given a course of treatments. She received 10 treatments, on alternate days, in a series comparable with that of any private patient. The dosage was usually 200 milliamperes for 0.1 or 0.15 second. Each treatment consisted of a major reaction with coma and convulsion lasting from 30 to 90 seconds. (Ninety seconds was the longest duration of any convulsion obtained with the electrical method.) Miss Darwin withstood her treatment course very well and her behavior was in no way altered by it.

Four days after the last treatment the animal was placed in deep ether narcosis and perfused with saline and sodium nitrite, and then with Zenker's solution to which formalin had been added. The brain was thus hardened in situ by the intravascular perfusion to avoid the manifold artefacts which occur when the fresh brain is handled and sliced. Later the brain was removed, cut in cross section, and stained. Dr Scharrer summarizes the findings as follows: "Sections from many regions of the brain revealed no lesions. Indeed, there were no cell destruction, no glial reactions, and no cellular changes in any of the sections."

This is the initial report of further work which has been planned.

C. Psychologic Studies This summer Dr Marguerite Hertz and Corinne Br. started a series of Rorschach tests taken before, during the course of treatment, and a month after the electro-coma treatment has been

concluded. The work is still in progress and the results of their findings will be published elsewhere.

D Electroencephalographic Studies A series of electroencephalographic tracings are being taken, parallel with the Rorschach tests, by Dr Charles Henry of the Brush Foundation. These studies were begun only recently.

COMMENT

The most significant observation from the clinical standpoint is the fairly high rate of improvement as well as the willingness of patients to take this treatment. Few patients experience the dread so common with metrazol. Coercion is, as a rule, not necessary. Indeed, not a few of the patients were treated in a general hospital with their consent and cooperation.

In the face of the practical results obtained, one cannot but pause and consider the nature of the illnesses and the mechanism by which electro-coma therapy brings about some relief of the symptoms. Let us approach this interpretation by listing certain observations and deductions.

A course of electro-coma treatment influences the mood of the patient first. Quite uniformly in all types of patients, there is a tendency for the saddened patient to become more cheerful.

In patients who are troubled by serious hallucinations and delusions, the improvement in mood brings about a change in the patient's attitude toward his hallucinatory experiences. They are pushed into the background, dismissed, and ultimately lost.

Recovery in mental function occurs rarely as a result of one or two treatments, but requires the accumulated benefits accruing from a series of treatments.

Recovery often takes place even though the patient has gone through a period of mental clouding with marked forgetfulness or confusion. These psychologic side actions apparently do not interfere with recovery. The road to recovery appears to be obscured by the clouding, but despite this delay, the clouding lifts and the goal of recovery is reached.

The treatment achieves its success through direct electrical or chemical alteration in brain functions. This observation is self-evident, particularly in view of where the electrodes are placed, the unconsciousness, and the changes in the electroencephalogram.

The therapeutic effect is not attained through the mechanism of fear, as patients who receive such treatment do not emphasize any terror reaction as was common with metrazol.

The incidence of recovery is highest in depressed patients¹⁰; there is improvement in many cases of schizophrenia, and there is a tendency toward improvement in manic states.

During the course of electro-coma treatment, one observes quite regularly a change in direction of interest and thought. In most psychoses the

patient is introverted, his major attention is upon his viscera, his moods, his past. Even the hallucinations and the stimuli outward either arise from within or are interpreted from an egocentric viewpoint. During the course of treatment the patient tends to look outward, to notice external stimuli, and to interpret them in line with reality. Recovery is thus not a gain in total brain function as much as an improvement in the direction of thought.

On the basis of these observations, one may make several conjectures. The first is that the brain is the seat of or the major link of all types of psychoses. Psychoses are caused by disturbances in brain function and are believed to be organic, even if the disorder cannot be histologically established (Elvidge and Reed,²¹ Katzenelbogen,²² Hoskins,²³ Angyal, Freeman, and Hoskins²⁴). The mechanism of recovery with electro-coma therapy depends upon an electrochemical change in brain cells. It appears as though each treatment damages the function of either cortical cells or association pathways. This effect tends to reduce or destroy those elements which are responsible for the abnormal direction of thought. The damage is reversible and there is a tendency for the abnormally functioning cells to regain their activity. Each succeeding treatment removes this tendency. In the depressions, when this change has been effectively brought about, there is recovery. In many types of schizophrenia, however, this improvement is temporary because there is an inherent destiny for a downward course. However, even in schizophrenia, so-called deterioration and dilapidation of thought are more apparent than real. One is sometimes surprised at the renewed intellectual interest in life which appears to be awakened in an apparently deteriorated patient as a result of shock therapy.

One must await the test of time before a true appraisal of the ultimate worth of the electro-coma method can be made. The permanence of recovery and the possibility of later complications will be determined only over a period of years. Scientific accuracy requires such a period. But the clinician who is faced with a sick patient must decide upon a course of treatment today. The practicing psychiatrist who examines a patient suffering from involutional melancholia, thin, trembly, agitated, and suicidal, cannot postpone action until an ultimate appraisal is made. He must use the best technique available at the time. At the moment electro-coma therapy appears to be the best available method for the treatment of many types of psychoses which have not responded to milder methods. The benefits to be gained and the dangers of inaction must be balanced against the hazards of the treatment. The advantages of electro-coma therapy over the hazards appear marked in involutional melancholia and many forms of depression. Likewise, the treatment is justified in many types of schizophrenia.

SUMMARY OF THERAPEUTIC RESULTS WITH ELECTRO-COMA THERAPY

No	Name	Age	Diagnosis	Result
1	F R	49	Paranoid schizophrenia	Excellent
2	I R	29	Hebephrenic schizophrenia	Good
3	P O	55	Schizodepression	Excellent
4	D P	57	Agitated depression	Good
5	E R	65	Involuntional melancholia	Excellent
6	B L	57	Endogenous depression	Excellent
7	S M	38	Endogenous depression	Excellent
8	W B	49	Agitated depression	Excellent
9	L R	25	Mania	Good
10	E P	23	Hebephrenic schizophrenia	Unchanged
11	S B	45	Endogenous depression	Excellent
12	B I	38	Paranoid schizophrenia	Doubtful
13	F F	36	Paranoid schizophrenia	Fair
14	I H	27	Paranoid schizophrenia	Unchanged
15	B C	67	Endogenous depression	Excellent
16	Z L	71	Involuntional melancholia	Good
17	N I	54	Endogenous depression	Fair
18	B H	36	Paranoid schizophrenia	Good
19	C E	38	Endogenous depression	Good to fair
20	C Ev	47	Involuntional melancholia	Good
21	F M	35	Hebephrenic schizophrenia	Temporary improvement
22	L J	19	Mania	Excellent
23	K C	46	Schizodepression	Fair
24	P E	30	Paranoid schizophrenia	Fair
25	D N	45	Schizodepression	Excellent
26	M M	29	Schizophrenia simplex (D P)	Fair
27	K A	34	Paranoid schizophrenia	Excellent
28	W N	55	Agitated depression	Fair (?)
29	M H	32	Schizodepression	Fair (?)
30	B J	61	Agitated depression	Fair
31	E B	45	Schizodepression	Good
32	T V	51	Agitated depression	Excellent
33	H R	30	Endogenous depression	Excellent
34	D M	57	Involuntional melancholia	Good
35	F J	46	Paranoid schizophrenia	Poor
36	K F	37	Paranoid schizophrenia	Fair
37	W C	41	Endogenous depression	Excellent
38	F M	36	Compulsion neurosis	Unchanged
39	R A	60	Involuntional melancholia	Poor (?)
40	S M	53	Paranoid schizophrenia	Unchanged
41	O E	34	Schizodepression	Fair
42	K F	55	Involuntional melancholia	Good
43	B I	20	Paranoid schizophrenia	Unchanged
44	W R	19	Hebephrenic schizophrenia	Fair
45	W G	49	Schizodepression	Fair
46	L K	63	Agitated depression	Fair
47	M B	26	Schizophrenia simplex (D P)	Fair
48	M D	29	Endogenous depression	Excellent
49	B S	43	Agitated depression	Good
50	C L	50	Agitated depression	Excellent
51	P H	45	Endogenous depression	Good
52	U M	58	Agitated depression	Excellent
53	H F	52	Schizodepression	Good
54	P M	51	Schizodepression	Excellent
55	K M	35	Cyclothymia	Good
56	L H	51	Paranoid schizophrenia	Poor
57	H H	34	Endogenous depression	Fair
58	W M	45	Paranoid schizophrenia	Fair (?)
59	P M	24	Paranoid schizophrenia	Too early to judge
60	V L	62	Endogenous depression	Fair (?)
61	D V	45	Schizodepression	Good
62	S F	40	Agitated depression	Excellent
63	A L	46	Endogenous depression	Good
64	L M	38	Endogenous depression	Good
65	M R	59	Agitated depression	Excellent
66	S B	50	Schizodepression	Fair
67	M M	30	Schizophrenia simplex (D P)	Poor to fair
68	S D	31	Endogenous depression	Good
69	K B	50	Endogenous depression	Good
70	T W	62	Involuntional melancholia	Good

posed in place of the label, "electro-shock therapy" "Minor," "moderate," and "major reactions" are used in place of the designations, "petit" and "grand mal"

The results of the electro-coma method have been found to be favorable. Certain of the psychologic side actions such as amnesia, periods of elation, and episodes of confusion are discussed. The complications are mentioned.

Certain general observations and a theoretical consideration of the mode of action of this method are offered.

For severe psychoses which do not yield to milder measures, electro-coma therapy is useful. It is particularly valuable for those psychoses in which depressed mood change is a major factor. It is worthy of trial in many forms of schizophrenia.

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CHRONIC CONSTRICTIVE PERICARDITIS; A FOLLOW-UP STUDY OF THIRTY- SEVEN CASES [†]

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ALTHOUGH constrictive pericarditis has been recognized for many years, it was not until the advent of modern thoracic surgery and its meticulous attention to technic and anesthesia that surgical treatment of the disease has been possible, with gratifying results in small but important groups of cases, gathered especially in Boston,¹ Nashville,² and Cleveland.³ An adequate historical review of the disease and its recognition has been given by White¹ and by Blalock and Burwell.² It is our purpose in this paper to present a follow-up study of 37 cases of constrictive pericarditis which have been seen

TABLE I
Group 1 Cases Cured by Operation

No	Name	Sex	Age†	Onset	Seen†	Heart Size	Rhythm	Calcium	Etiology	Resection
1	C S *	F	19	1911	1925	normal	normal	0	?	7/18/28
2	B K *	F	10	1922	1931	+1 cm	normal	+	?	11/16/33
3	L F *	F	30	1931	1933	normal	normal	0	?	4/6/33
4	C F *	M	19	1931	1933	normal	normal	0	pneumonia c pleurisy	4/22/33
5	L C *	M	12	1933	1933	normal	normal	+	?	7/12/33
6	O P	M	28	1935	1936	normal	normal	0	?	10/8/36
7	S L	M	26	1937	1938	normal	normal	0	?	6/29/38
8	H W	F	44	1937	1939	+1 cm	normal	+	?	10/9/39

Addendum

9 Case 4 of Group 5, I B, really belongs also in Group 1, as does also
10 Case 2 of Group 2, G P, and as will doubtless also, when adequate time elapses, several more

11-14 Cases 5-8 of Group 2

* Indicates cases reported by P D White in 1935

† Age and year when first seen by us

at the Massachusetts General Hospital, in whom the diagnosis has been made clinically and confirmed in all but a few by operation or by autopsy examination

In 1928 Churchill carried out the first successful operation for this condition in this country,^{4, 5} and in 1935 White¹ reported 14 other proved cases seen at the Massachusetts General Hospital. Twelve had been operated upon, three had not. Two more cases had been recognized at this hospital prior to the first operation but not confirmed at that time, both have died, and autopsy done on one of the two disclosed the presence of the disease.

Since that report in 1935, 20 additional cases have been studied, 16 of

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which have had pericardial resections (one of the 16 at another hospital), thus making a total of 37 patients seen at this hospital. Nineteen are living, 17 are dead, and one has not been examined lately and may be either living or dead. Twenty-eight of the group have been operated upon, nine have not.

Of the 37 patients, 25 were males, 12 were females. The ages ranged from 10 to 59 years. The average age of the entire group was 30.2 years, of those operated on 28.8 years, and of those not operated on 45.5 years.

FOLLOW-UP ANALYSIS

For clinical evaluation of results, we have grouped the cases according to whether they (1) have been cured by operation, (2) have been improved by operation, (3) have died of the disease itself, (4) have died as a result of operation, (5) have died of complications, (6) are living without operation, or (7) have not been heard from in recent years.

*Group 1 Cured by Operation** In this group at the present time there are eight cases, who were operated on from two to 13 years ago. These patients have all been seen or heard from in the past three months. In no case is there any limitation of activity because of a cardiac disability. They are able to carry on a normal life, and are in no way inconvenienced by the post-operative defect. Three of these patients show a just visible jugular pulse in the sitting position. Two patients were not examined, and although it is not known whether a venous pulse is visible at the present time, their general condition is excellent. Of the group reported in 1935 by White,¹ one patient (D G) who was thought to have been cured has since developed an enlarged heart, some slight edema of the legs, and an enlarged liver. However, she has no dyspnea, and is able to lead a fairly normal life, if exertion is not excessive. She is, therefore, included in the following group.

Perhaps the most instructive and interesting of all our cured cases is our very first patient (C S, now C S O'N) referred by one of us (P D W) in the summer of 1928 to Dr. Churchill for pericardial resection. She was the first case successfully operated upon for this condition in this country. She has remained in excellent health ever since, was married a few years ago, and went through a normal pregnancy without any difficulty and delivery of a healthy son by forceps on March 1, 1941.

Group 2 Improved by Operation In this group there are eight cases. One patient (D G) is mentioned above. A second patient (G P) has had two operations. Following the first operation he was greatly improved over his former condition, but continued to have some dyspnea and edema, and abdominal fluid collected which had to be removed by paracentesis every month or two. Two years after the first operation, further pericardial resection was carried out, and since then the patient has been able to carry on a

*Later note, August, 1942. Since this was written above, cases 5 to 8 of Table 2 have completely recovered, so that they plus case 4 of group 5 and case 2 of group 2, form an addition of 6 cases to Table 1, raising the cured cases from 8 to 14 in number.

TABLE II
Group 2 Cases Improved by Operation

No	Name	Sex	Age	Onset	Seen	Heart Size	Rhythm	Calcium	Etiology	Resection	Remarks
1	D G *	F	11	1935	1935	+2 cm	normal	0	?	2/27/35	Slight edema, enlarged heart and liver
2	G P	M	43	1934	1935	normal	aur fib	+	?	10/18/35 10/21/37	Slight dyspnea on exertion
3	P C	M	34	1931	1938	+2 cm	aur flutter	+	?	3/ 7/38	Last seen by us in 1938
4	W R	M	35	1936	1939	+2½ cm	aur fib	+	?	2/ 9/40	Slight congestive failure, gallop rhythm
5	T P	M	24	1935	1940	+2½ cm.	normal	0	?	11/12/40	Too early to evaluate results completely
6	A T	F	40	1938	1941	normal	normal	+	?	5/17/41	Probably cured
7	R C	M	30	1935	1941	normal	aur fib	+	?	7/ 2/41	
8	E S	F	24	1940	1941	normal	normal	0	TB	10/20/41	

* Case reported by P D White in 1935

NB Later note, August, 1942
Table 2 to Table 1

Cases 5 to 8 inclusive have shown complete recoveries and so should be transferred as "cures" from

TABLE III
Group 3 Cases Who Died Primarily of the Disease Itself

No	Name	Sex	Age	Onset	Seen	Heart Size	Rhythm	Calcium	Etiology	Treatment	Remarks
1	M T	M	59	1913	1914	+4 cm	aur fib	0	?	diuretics belly taps	Died in congestion in 1922
2	A A	M	53	1924	1926	+1 cm	aur fib	0	?	belly taps	Died in congestion in 1938
3	A G *	F	32	1933	1934	normal	normal	0	?	chest taps belly taps	Died in congestion in 1934 Large septal defect also found at autopsy
4	G H	M	25	1936	1937	normal	normal	+	? TB	Resection 3/22/37	Died of tuberculosis in 1937
5	M S	F	54	1938	1940	normal	aur fib	+	?	Resection 4/12/40	Died in congestion four months post-operatively
6	J G	M	45	1913	1938	normal	aur fib	+	?	diuretics belly taps	Died in congestion in 1940

* Case reported by P D White in 1935

quiet life, though at times he is a little troubled by slight dyspnea on exertion. The venous pressure is now at the upper limits of normal. He has not required abdominal taps since the second operation, and may actually be considered a clinical cure. One patient (P C) who was successfully operated upon has not been heard from since four months after his pericardial resection three years ago, but at that time he reported that he was feeling quite well, that evidence of edema and ascites had practically disappeared, and that there was no dyspnea on exertion. It is probable that this patient represents a complete cure, but without further information it is deemed unwise to include him in Group 1. One patient (W R) operated upon in 1940 responded very well and was able to return to his work four months following operation. However, when seen two months ago, he showed some enlargement of his heart, chiefly in the region of the right ventricle, and there was a marked gallop rhythm over the right ventricle. This was believed to represent dilatation of the right ventricle following decortication. He was given digitalis, and improved somewhat, although the gallop is still present. In addition, he has developed an aortic diastolic murmur of unknown etiology since the operation. In spite of these sequelae, the patient seems able to carry on a moderately active life.

The remaining four patients of this group have all been operated upon within the last year, and we believe that it is too early as yet completely to evaluate their condition, but from the progress that each has made, we are under the impression that these remaining four cases will be included in Group 1 at a later date as cured cases.

One case (J N) reported as belonging to this group in 1935 by White¹ has since died, and will be discussed later. All this group of cases improved by operation has been seen since 1938.

Group 3 Cases Who Died Primarily of the Disease Itself There are six patients included in this group, five having been added since 1935. Two of the three original cases (J M, J B) died following operation and, therefore, are shifted to Group 4. Both showed definite evidence of tuberculosis of the pericardium. The third case (A G) was not operated upon, but died in acute heart failure before operation. At that time it was interesting to note that this patient showed a prolonged P-R interval (0.22 second) with prominent P-waves in Lead II, and is the only one in the entire series who showed this abnormality. One year later while the autopsy specimen was being mounted, it was discovered that there was a very large septal defect present in addition to the constricting pericarditis. This septal defect probably accounted for the unusual changes in the electrocardiogram, and perhaps for the very slight enlargement of the heart which was present.

Of the five additional patients, two were operated upon, and three were not. Of those subjected to surgery, the first (G H) did poorly after a stormy postoperative course, and after a second admission to the hospital two months later was discharged to a tuberculosis sanatorium where he subsequently died of tuberculosis. It was believed that operation on this patient

stirred up activity in the mediastinal glands, although on section of the pericardium there was no evidence of old or recent tuberculosis, except for focal necrosis, which was not sufficient for a pathological diagnosis of tuberculosis. The second patient (M. S.) improved only slightly after operation, and during the succeeding four months required monthly abdominal paracenteses. She was readmitted to the hospital, suddenly went into acute heart failure, and died despite all efforts to save her. There was no evidence of tuberculosis at autopsy.

Of the three remaining patients, not operated upon, two were cases not discussed in the original report by White¹. The first patient (M. R.) was originally seen in 1913, when diagnoses of hepatic cirrhosis, ascites, and cardiac hypertrophy were made. This patient was followed for nine years, during which time the diagnosis was changed to chronic constrictive pericarditis. During the nine years of observation the patient had repeated abdominal paracenteses, and on his last entry died very shortly after admission in acute and chronic congestion. No autopsy was performed. The second patient (A. A.) was followed for 14 years, but because of his age and only moderate disability, operation was not advised even though the condition later became more advanced. He had many abdominal paracenteses and died in 1938 in congestion. Autopsy confirmed the clinical diagnosis. The third patient (J. G.), seen since our original series was published, was first examined in 1938, at which time operation was not considered because the condition was mild. He was seen the following year, during which time he had a marked progression of the disease. He was then admitted in preparation for operation. However, he did not respond sufficiently well to treatment to warrant the operative procedure, and was discharged for further care, to return for operation at a future date. However, he failed to make the expected response and died in congestion. Autopsy confirmed the clinical diagnosis.

Group 4 Cases Who Died as a Result of Operation. In this group there are five cases, three of which (J. B., J. H., J. M.) were included in the 1935 report in Groups 3 and 4, but have been placed in the present Group 4, because their deaths were due essentially to the surgical procedure. Of the two additional cases, one (S. G.) died, on the operating table, of acute dilatation and failure of the right ventricle when the pericardium was removed. The second case (V. G.), although seen here, was operated upon at another clinic and died two days postoperatively following pulmonary embolism. It was of interest that in this case there was a core of calcification which extended from the pericardium through the myocardium to the endocardium at one point. These five deaths in the series of 28 cases submitted to operation result in an operative death rate of 18 per cent.

Group 5 Cases Who Died of Complications. In this group are six cases, three of which were reported in 1935. The third case (J. H.) originally in this group has now been included in Group 4. The third case in the present group is that originally reported as improved by operation (J. N.). In

TABLE IV
Group 4 Cases Who Died as a Result of Operation

No	Name	Sex	Age	Onset	Seen	Heart Size	Rhythm	Calcium	Etiology	Resection	Remarks
1	J B *	M	23	1931	1931	+3½ cm	normal	0	TB	1/ 4/31	Died one day postoperatively
2	J H *	M	52	1931	1933	+2 cm	aur fib	+	?	9/20/33	Died of bronchopneumonia, pulmonary edema six days postoperatively
3	J M *	M	36	1934	1934	+4 cm	normal	0	TB	4/ 2/34	Died on operating table
4	S G	F	13	1934	1936	normal	normal	0	?	5/27/36	Died on operating table, acute right ventricular dilatation and failure
5	V G †	M	41	1929	1938	normal	normal	+	?	8/20/38	Died of pulmonary embolism two days postoperatively

* Cases reported by P D White in 1935

† Operated on at another clinic

TABLE V
Group 5 Cases Who Died of Complications

No	Name	Sex	Age	Onset	Seen	Heart Size	Rhythm	Calcium	Etiology	Treatment	Remarks
1	L A *	M	18	1930	1930	+3 cm	normal	0	TB	Resections 4/16/31 2/23/34	Died of acute pancreatitis one month after second operation
2	II P *	F	31	1928	1931	+1 cm	normal	+	sepsis	Resection 4/29/31	Died of general sepsis, one year post-operatively
3	J N *	M	16	1921	1932	+2 cm	aur fib	+	with pleurisy pneumonia	Resections 9/27/32 11/16/33 Omentopexy 3/30/34	Died suddenly one day after removal of emboli of common iliac arteries and right femoral artery, 1940
4	I B	M	47	1935	1935	normal	normal	0	?	Resection 11/ 6/35	Apparent cure Died of type III pneumococcus pleurisy one year postoperatively
5	M B	F	34	1928	1938	+2 cm	aur fib	+	?	Resection 5/16/38	Died of bronchopneumonia two years postoperatively
6	W M	M	33	1934	1936	normal	normal	0	TB	Diuretics	Died of miliary tuberculosis, 1936

* Cases reported by P D White in 1935

this latter case, two pericardial resections and an omentopexy had been performed, but the patient continued to have large accumulations of fluid in the abdominal cavity, requiring frequent paracenteses. He was able, however, to carry on moderate activity, as long as the abdominal fluid was removed at frequent intervals. When retiring one evening he suddenly experienced numbness and coldness of the lower extremities. A diagnosis of peripheral emboli of the legs was made, and emboli were removed from the left and right common iliac arteries, and from the right femoral artery. One day following the operations he suddenly began to gasp for breath and died in a few minutes. The autopsy protocol describing the heart, lungs, and mediastinum is as follows:

An area (measuring approximately 6 by 5 cm) of the lower anterior portion of the pericardium had been surgically removed. In its place is a moderate amount of fibrous scar tissue which is adherent to the under surface of the operative wound, but which separates easily with blunt dissection. The remaining portion of the anterior parietal pericardium is for the most part fibrous and adherent to the visceral layer. The upper two-thirds of the left antero-lateral portion of the pericardial cavity is completely obliterated by irregular confluent masses of calcium, extending cephalad to involve the base of the aortic valve and forming a large plaque measuring 9 by 6 cm in extent. The outer surface of the plaque is covered by fibrous tissue which in turn is adherent to the mediastinal parietal pleura of the left lung. This plaque extends somewhat posteriorly to impinge by external pressure upon the lumen of the mitral valve. There is no calcification of the pericardium in the region of the apex of the left ventricle. There is a similar but smaller zone of pericardial calcification involving the anterolateral aspect of the right ventricle over an area measuring 9 by 4 cm. On this side, however, the calcification extends almost to the apex of the right ventricle, but does not extend up as high as the level of the pulmonary artery. Posteriorly, the pericardium is free from calcification.

Heart The heart is not dissected free from the pericardium and the lungs, but is opened in situ. The myocardium is red-brown. The right ventricular wall measures 3 to 4 mm in thickness, the left, 13 to 15 mm. The left auricle is moderately enlarged, and measures roughly 8 by 6 by 4 cm. The remaining cavities and the columnae carnae are essentially negative. The lateral aspect of the mitral valve is pressed on externally by the calcified pericardium, resulting in a slight stenosis. The aortic valve is moderately thickened and shows slight interadherence of the cusps at their commissures. The other valves are essentially negative. The coronaries are negative.

There was no evidence of a pulmonary embolus of such a size that death could be attributed to it.

It is interesting that in this case there was almost complete constriction of the left ventricle together with an impingement by a calcified pericardial plaque on the lumen of the mitral valve from outside the heart, which factors undoubtedly accounted for much of the lack of improvement following pericardial resections and omentopexy. This situation had been suspected before death. It is also of interest that chronic rheumatic endocarditis with slight aortic stenosis was present. This is the only case in the entire series in which rheumatic heart disease has been found. There was no pulmonary embolus of sufficient size to account for the sudden death.

The fourth case (I B) had apparently been cured when seen one year following operation. He had been able to carry on a fairly normal life until about five days before his last hospital admission when he suddenly developed a respiratory infection followed by dyspnea and cyanosis. In spite of vigorous treatment he died. Postmortem examination showed pyopneumothorax, type three pneumococcus, and pulmonary congestion, but no frank consolidation.

The fifth case (M B) underwent pericardial resection in 1938, and was seen again in 1939, when it was noted that she had very little, if any, improvement from operation, and it was advised at that time that if there were no definite improvement in the next few months another operation should be attempted in the hope of further improving her condition. However, the patient did not return for further study, and she died elsewhere of bronchopneumonia. An autopsy showed, in addition to the constrictive pericarditis, healed obliterative pleuritis, healed fibrous peritonitis, a tubercle in one lung, apparently healing, and cardiac hypertrophy.

The sixth patient (W M) was first seen by us in 1936, after a pericardial tap had revealed slightly bloody fluid with tubercle bacilli demonstrated in the smear. The patient was advised to have a period of prolonged bed rest, both for treatment of the active tuberculosis, and in the hope that he could be adequately prepared for operation after subsidence of the active infection. However, the patient failed to improve, and died four months later. Postmortem examination showed miliary tuberculosis.

Group 6 Patients Living, Not Proved by Operation There are three patients in this group, two of whom have been seen since the original report of cases from this hospital. The first patient (W B) included in the original reports, and now 68 years old, has written that he is feeling well, with only slight restriction of activity. He is continuing with his medical practice, "feeling better than 10 years ago." There were some slight hepatic congestion and engorgement of the neck veins. He has shown pericardial calcification by roentgen-ray. His most recent letter is of such great interest and importance in showing that operation is not essential in every case that it is herewith quoted in full.

Your letter of inquiry received. Am glad to tell you I am doing very well indeed.

Exercise tolerance Well, I think I can get around just as well now as I did 10 years ago. Can handle one flight of stairs very well and two flights also without discomfort. Outside, I don't walk more than a block. Don't choose to walk but can do so if put to it.

Edema During the last nine months have had no edema at all anywhere, at any time of the day or night.

Irregular heart action My heart is still irregular but does not bother me as it did except when I hurry, get excited or overdo in any way, so I am careful. In fact, I think in the morning after a good night's rest and sleep, my heart is regular and can go for several days without being conscious of a flutter at all.

Liver enlargement Have forgotten about the old liver now. For the last half-century or a little less, that gave me a lot of distress enlarging and contracting with

varying degrees of cardiac weakness from an inch or so below the costal border down to the umbilicus. Don't believe liver is enlarged at all now. Have no sensation of any fullness in that region now.

Engorgement of veins of neck, particularly when in the recumbent posture That always gave me a lot of distress down through the years. It was my habit to stuff a corner of the pillow firmly under my jaw under-side to relieve that discomfort in order to get sleep. Don't have to do that now. So, doctor, that is how I am at the present time. People tell me I look as young as I did 20 years ago. Have had no setbacks recently of infections in the past eight or ten years. That means a lot. Don't think I could stand much of an infection. Nine months ago, in February of this year, had a coryza. That crept down to the bronchi and gave me a troublesome cough. I felt quite sick. No temperature. Had some edema then in face and over sacrum and in ankles when I got on my feet. That was nine months ago.

I think I had also some crepitations at base of lungs. Sent for my doctor. He said, "Get right to the hospital to bed and stay there for four weeks. Absolute rest in bed, no getting up for anything. Getting up once will set you back one week at \$5.00 per day." So that was a pretty good incentive to obey orders. For the first week I slept all night and dozed most of the days between feedings. After three weeks, I felt so good I kicked over the traces, got up, sat around for one day, and went home the next. My legs were weak from non-use, but all the edema had vanished and I haven't had any since, and that's a record for me, and since then, have been, as I told you above.

A recapitulation of the whole condition for the past 50 years In the fall of 1893, went to Baltimore to resume medical studies. In the winter of 1894 had a subacute pleurisy. Continued my studies and attended class, holding on to my right side. Saw Dr. Latimer, a prominent physician in Baltimore then, regarding this. He examined me and prescribed Beechwood Creosote. Evidently thought I had tuberculosis. Returned home to Nova Scotia after college closed.

I then became severely ill with an acute febrile condition. In bed three months. After getting up, had a lot of diopsy and a large pulsating liver. Was treated for typhoid fever. In the fall of 1894, went to Boston and consulted Dr. Frederick Shattuck. Was in Massachusetts General Hospital one month, the month of November, 1894, under Dr. Shattuck's care. Had a lot of swelling then and enlargement of the liver. Dr. Shattuck's diagnosis was chronic hepatitis due to extension of the pleurisy through the diaphragm into the liver. In the fall of '95 returned to Baltimore to resume medical studies. I still had all that winter a lot of swelling in my legs. Graduated in medicine in 1896. I returned to Nova Scotia and did a hard country practice for 18 years. Continued getting better as the years went by but at no time was I free from edema of the legs.

In 1914, the beginning of the first year of war, I enlisted in the army. That was too strenuous for me. In the winter of 1917, had an acute heart failure, in bed one year. Gradually pulled out of that. In 1923, began having attacks of auricular fibrillation. In 1929, another attack of heart failure. In bed one year. About that time I first saw you, and you know how I have been since then.

When you next want to know how I am getting on, I can only hope that I will be here to answer you.

The second patient (C. A.) was seen one year ago, having had some slight edema, and swelling of his abdomen from time to time during the previous four years. However, his condition one year ago was not considered serious enough to warrant operation, and he was discharged from the hospital. He was seen by us again one year later, and was doing well on a

TABLE VI
Group 6 Cases Living, Not Proved by Operation

No	Name	Sex	Age	Onset	Seen	Heart Size	Rhythm	Calcium	Etiology	Treatment	Remarks
1	W B *	M	57	1917	1930	+1 cm	aur fib	+	?	Diuretics Digitalis	Slight restriction of activities
2	C A	M	50	1936	1940	+1 cm	aur fib	+	?	Diuretics Digitalis	Feeling well Slight limitation of activities
3	A J	M	36	1921	1941	+1 cm	aur fib	0	?	Diuretics	Moderate limitation of activities

Group 7 Case Not Examined Recently

No	Name	Sex	Age	Onset	Seen	Heart Size	Rhythm	Calcium	Etiology	Treatment	Remarks
1	A B *	M	45	1932	1932	+1½ cm	aur fib	+	?	Diuretics Digitalis	Last seen in 1934

* Cases reported by P D White in 1935

maintenance dosage of digitalis, and quinidine for occasional attacks of palpitation. Only occasionally was there any edema, and the patient thought he was feeling better than he had previously felt, although occasional rest periods were found helpful. Operation was not advised.

The third patient (A J) had had a story of about 20 years of slight edema and shortness of breath which had become somewhat troublesome in the past year, due to tachycardia incident to the onset of auricular fibrillation. Under digitalis therapy his heart rate fell, and he improved and was able to continue with his work with some limitation. It was thought that there was not enough disability to warrant the risk of operation at the present time. This patient was seen only a few months ago for the first time.

Group 7 Case Not Recently Examined There is one patient (A B) in this group who has not been heard from since the original report, efforts to locate him have failed. This patient was not operated upon.

ETIOLOGY

Among our original 15 cases which were reported in 1935, the etiological factors were tuberculosis in three cases, pneumonia with polyserositis in two, sepsis in one, and unknown or questionable in nine. Among the additional 22 cases, the etiological factors were tuberculosis in two, and unknown or questionable in 20, five of this latter group had had a definite history of pleurisy (three cases) or pericarditis (two cases). It is of interest that one of the cases without a known etiological factor (J G) had suffered from an attack of rheumatic fever with pancarditis 25 years before he was first seen by us, and had had several bouts of rheumatic fever since the first infection, but at autopsy there was no evidence of any rheumatic valvular disease or shortening of the chordae tendineae. It seems unlikely that rheumatic fever played any important part in the production of the constricting pericardium, since almost certainly some damage to the heart valves or the chordae tendineae would be expected if such severe damage of the pericardium were caused by rheumatism. One other case (J N) showed rheumatic endocarditis with slight aortic stenosis, it is possible that rheumatism may have been the etiological factor in this case, but it is more likely that the rheumatic heart disease was a coincidental finding and that an attack of pneumonia was the underlying cause. One other case (M B) had had an attack of rheumatic fever 10 years prior to operation, but at autopsy there was no evidence of any rheumatic heart disease. These results are in accord with an autopsy study of 6100 cases at the Massachusetts General Hospital, reported by Sprague, Burch, and White,⁶ in which there were only six cases of adherent pericardium without valvular disease who gave a history of rheumatic fever, and in none of whom Pick's disease was present. Also a follow-up study of 1500 cases of rheumatic fever at the House of the Good Samaritan in Boston has revealed no case of chronic constrictive pericarditis (personal communication, E F Bland, 1941). Although several authors have mentioned rheumatic fever as being an etiological factor in the pro-

duction of constrictive pericarditis (Trout, Smith and Willius, and Rothstein, cited by Blalock and Burwell²), we are quite sure that rheumatic fever is rarely, if ever, an etiological factor

One case (A G), cited above in Group 3, had, in addition to the constrictive pericarditis, a congenital defect, consisting of a large patency of the septum

Tuberculosis appears as a less common factor in our series than in that of Blalock and Burwell, accounting definitely for only 14 per cent of our cases (5 of 37), whereas it accounted for 64 per cent of theirs

SIZE OF HEART AREA

In this study the size of the cardiac area has been of interest. Of the total number of 37 cases, 19 had slightly to moderately enlarged areas, i.e., from 1 to 4 cm over normal in transverse diameter during life, and 18 had normal sized hearts. The measurements were made by roentgen-ray or physical examination, or both. In addition, some of the cases (10 in all) showed murmurs, systolic in all except one instance (see table). Calcification of the pericardium was encountered in 16 cases. These findings are tabulated below

TABLE VII

Incidence of Heart Area Enlargement, of Murmurs and of Pericardial Calcification in Our Total Series of 37 Cases

	Number of Cases	Murmurs	Calcification
1 Enlarged heart areas			
Living, operated on	6	{ 1-apical systolic 1-aortic diastolic	5
Living, not operated on	3	0	2
Dead, operated on	7	{ 1-apical, aortic systolic 1-apical systolic	3
Dead, not operated on	2	2-apical systolic	0
? Living or dead	1	0	1
Total	19	6	11
2 Normal sized hearts			
Living, operated on	10	2-apical systolic	3
Living, not operated on	0		
Dead, operated on	5	1-apical systolic	1
Dead, not operated on	3	1-apical systolic	1
Total	18	4	5

From this it can be seen that slightly over half of the patients had enlarged heart areas. Forty-three per cent of the cases had calcification of the pericardium, but of those with normal sized hearts only five (28 per cent) had calcification, whereas of those with enlarged heart areas, 11 (60 per cent) had calcification. The difference in the presence or absence of murmurs in the two groups is not striking. The one aortic diastolic murmur developed one year following operation. None of the apical systolic murmurs were of marked intensity. From the figures presented above it would

appear that those patients with normal sized hearts have a somewhat better prognosis than those with enlarged heart areas. Those with calcification are more likely to show enlargement.

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiograms were studied in these cases with respect to rhythm, axis deviation, voltage changes, and T-wave changes.

1 *Rhythm* The arrhythmias in the various groups are tabulated, together with heart size and calcification.

TABLE VIII
Incidence of Arrhythmias

		Enlarged Heart Area	Calcification	Normal Heart	Calcification
1	Normal rhythm				
	Living, operated on	12	4	3	8
	Living, not operated on	0	—	—	—
	Dead, operated on	8	5	1	3
	Dead, not operated on	2	0	0	2
		—	—	—	—
		22	9	4	13
2	Auricular fibrillation				
	Living, operated on	3	1	1	2
	Living, not operated on	3	3	2	0
	Dead, operated on	4	3	2	1
	Dead, not operated on	3	1	0	2
	? Living or dead	1	1	1	0
		—	—	—	—
		14	9	6	5
3	Auricular flutter				
	Living, operated on	1	1	1	0

From the above it can be seen that normal rhythm is more common than auricular fibrillation or flutter, and was present in two and a half times as many normal sized hearts as was fibrillation or flutter. However, the presence of an arrhythmia was noted two and a half times as frequently in the enlarged hearts as in the normal sized hearts. Also, abnormal rhythms were present three times more frequently in cases which showed calcification than in those which did not.

The patient (P C) with auricular flutter continued to have this arrhythmia for three weeks after operation, which was the time of the last tracing recorded.

One patient (A T) showed transient auricular flutter a few days post-operatively, but normal rhythm returned following the administration of quinidine, and has remained in the subsequent six months.

One patient (C A) when first seen showed a shifting pacemaker, but when seen one year later showed auricular fibrillation. He had not been operated upon.

One other patient (J N) developed auricular fibrillation one year after the first operation. The arrhythmia persisted until his death.

2 Axis Deviation Although axis deviation in the presence of the low voltage found in most of the electrocardiograms is not of great importance, it was found that one patient (L F) shifted from a slight right axis deviation to normal eight and a half years after operation, without much change in voltage, five cases shifted from normal to slight right axis deviation (O P, G H, J N, I B, M B) three months to five years following operation. Two of these (J N and M B) showed auricular fibrillation. One patient (M T), not operated upon, shifted from left axis deviation to a 90 degree angle over a period of five years. He also showed right bundle branch block, and was the only patient of the 37 with widened QRS complexes. In none of the cases, however, were these changes striking.

Follow-up electrocardiograms were obtained on 30 of the 37 patients, 22 who had been operated on, and eight who had not. For purposes of discussion, the QRS complex changes and the T-wave changes of the classical leads will be discussed separately.

3 Low Voltage Low voltage of the QRS complexes (and T-waves) was found in all three classical leads in 18 of the 28 cases operated upon. Following operation, a slight increase in voltage, averaging 2 mm, was found in two cases (B K, R C). Practically no change was found in 12 cases. The remaining four cases (C S, L A, J H, J N) showed lower voltage after operation. These figures indicate that there is neither a marked nor consistent change in the voltage of the QRS complex following pericardial resection, and that the voltage usually remains low after operation.

Of the eight cases not operated upon, low voltage was present in all three leads in four. When the eight cases were seen later, four had remained practically the same (two months to two years after the original electrocardiogram), and four showed lower voltage throughout (from one to 13 years after the original electrocardiogram).

4 T-Waves The T-wave changes in Leads I and II, before and after operation, are best shown by the following table.

TABLE IX
The T-Waves in the Electrocardiograms of Cases Operated Upon

Before Operation		After Operation					
	Number of Cases	Normal	Low	Flat	Diphasic	Inverted	Unchanged
Normal T ₁	1	0	1	0	0	0	0
Low T ₁	12	1	0	2	2	3	4
Flat T ₁	1	0	0	0	1	0	0
Diphasic T ₁	1	0	0	1	0	0	0
Inverted T ₁	7	0	1	1	0	0	5
Normal T ₂	1	0	0	0	1	0	0
Low T ₂	5	0	0	3	0	1	1
Flat T ₂	0	—	—	—	—	—	—
Diphasic T ₂	6	0	1	1	0	3	1
Inverted T ₂	10	0	0	1	2	0	7

Of the above 22 cases in which follow-up electrocardiograms were obtained, six had both T_1 and T_2 inverted. Of these, four showed inverted T-waves in Leads I and II after operation. Of the remaining two, T_1 remained inverted in both cases, T_2 became diphasic in one case and flat in the other.

The one case in which a flat T_1 became normal after operation was one of those in whom the voltage also became normal (L C). Of the 22 cases, in six T_1 became higher (including that in which T_1 returned to normal), and in 16 cases T_1 remained unchanged or became lower. From these results it would seem apparent that there is no consistent or characteristic change of the T-wave in Lead I or II following pericardial resection.

Of the eight cases not operated upon in which follow-up electrocardiograms were obtained, seven showed the following changes in the T-waves of Leads I and II:

TABLE X
T-Waves of Electrocardiograms of Cases Not Operated Upon

Original Tracing		Follow-up Tracing						Time Interval
	Number of Cases	Normal	Low	Flat	Diphasic	Inverted	Un-changed	
Low T_1	4	—	—	1	1	1	1	1 mo to 13 yrs
Flat T_1	2	1	1	—	—	—	—	2 mo to 2 yrs
Diphasic T_1	0	—	—	—	—	—	—	—
Inverted T_1	1	—	—	1	—	—	—	9 mo
Low T_2	2	1	—	—	1	—	—	2 mo to 1 yr
Flat T_2	1	—	—	—	—	—	1	2 yrs
Diphasic T_2	3	—	—	1	—	1	1	1 to 13 yrs
Inverted T_2	1	—	—	—	—	—	1	9 mo

These figures show that in four cases there was some slight increase of the T-waves during the period of observation of the cases not operated on. The changes do not appear consistent enough to warrant any conclusion regarding the change in T-waves of Leads I and II during the progression of the disease.

The eighth patient showed right bundle branch block in all tracings, with upright T_1 and inverted T_2 in the first tracing. The last tracing, five years later, showed a marked decrease in voltage, and T_1 had become inverted and T_2 had become upright. The T-wave changes cannot be interpreted accurately in this case with reference to the constricting pericarditis, because of the complicating right bundle branch block.

In three cases, T_3 became normal after operation (O P, A T, E S). In one case (A G), not operated upon, T_3 became normal two months after the original tracing. In all other cases T_3 remained flat or inverted after either operation or observation.

We would emphasize herewith the importance of the electrocardiogram in the diagnosis of chronic constrictive pericarditis, it was abnormal in all

our cases, the abnormality consisting of low voltage of the QRS waves or abnormal T-waves, or both

SUMMARY

Thirty-seven cases of constrictive pericarditis are presented as a follow-up study. The later results of 15 of the cases which were reported in 1935 are given, together with a brief clinical survey of the course of 22 additional patients seen at the Massachusetts General Hospital. The age, sex, etiological factors, clinical data, and electrocardiographic findings are presented

(1) *Age* The ages ranged from 10 to 59 years. The average age of those operated upon was 28.8 years, of those not operated upon 45.5 years.

(2) *Sex* Male, 25, female, 12.

(3) *Etiology* Tuberculosis, five, sepsis, one, pneumonia with polyserositis, two, unknown or questionable, 29. Of this latter group three cases had had known previous pleurisy, and two had had known acute pericarditis.

(4) *Heart size* Nineteen, or 54 per cent, of the patients reported had enlarged heart areas, from 1 to 4 cm. over normal in transverse diameter. Of these, five or 26 per cent, had apical systolic murmurs, one had an aortic diastolic murmur. Eighteen, or 46 per cent, had normal sized hearts. Of these, four, or 22 per cent, had apical systolic murmurs.

(5) *Calcification of the pericardium* Sixteen, or 43 per cent of the total number of cases in this series, had calcification of the pericardium. Eleven, or 30 per cent, had enlarged heart areas with the calcification of the pericardium, and five, or 13 per cent, had normal sized hearts with calcification of the pericardium.

(6) *Electrocardiographic Findings*

(a) Normal rhythm was present in 22, or 60 per cent, of the series. Auricular fibrillation was present in 14, or 37 per cent, of the series. Auricular flutter was present in one, or 3 per cent, of the series. Normal rhythm was found to be present two and a half times more often than was auricular fibrillation or flutter in the cases with normal sized hearts. Arrhythmia was present two and a half times as frequently in the case of the enlarged heart areas as in the case of the normal sized hearts.

(b) Axis deviation was found to be normal in almost all of the patients.

(c) Low voltage of the QRS waves in all three classical leads was found in 22 cases, or 60 per cent, of the whole series. Following operation, normal voltage of the three leads was found in two, or 7 per cent, and these two cases had had normal voltage of the QRS waves in two of the three classical leads before operation.

(d) Abnormal T-waves of two or three of the classical leads were found in all cases in this series. Following operation none of the T-waves became

normal in more than one lead; three cases showed normal T-waves in Lead III, and only one case showed normal T-waves in Lead I

(e) The electrocardiogram was abnormal in every case

(7) *Follow-up Status* (August, 1942) Twenty-eight of the 37 patients have had pericardial resection

(a) Fourteen of these 28 were clinically cured although in a few cases slight increase in venous pressure above the average normal remains, and one of the 14 died of other cause (pneumococcus pleurisy) one year post-operatively

(b) Three others were much improved by the operation

(c) Two died primarily of the disease itself, one of tuberculosis soon after the operation and one in congestion four months post-operatively

(d) In five the death was related to the operation, 2 of the 5 succumbing on the day of operation, one died one day post-operatively, one died of pulmonary embolism two days post-operatively, and one died of bronchopneumonia six days post-operatively

(e) Four died of other complications one of acute pancreatitis one month after the second operation, one of general sepsis one year post-operatively, one of bronchopneumonia two years post-operatively, and one of arterial embolism seven years post-operatively

(8) Nine cases did not have pericardial resection

(a) Three were so mild that operation was not thought necessary

(b) Three were too sick to undergo operation

(c) One died of miliary tuberculosis before the operation could be carried out

(d) One died before this series of operations was started

(e) One case has been lost sight of

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SURGICAL TREATMENT OF HYPERTENSION (RESULTS IN FIFTY-FOUR CASES)*

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DURING the last 10 years 54 patients with hypertension have been operated upon at the Lahey Clinic. Sufficient time has elapsed to justify an evaluation of the results to date in all of these cases. The effectiveness of surgery in some cases of hypertension has been reported by Allen and Adson,¹ Crile,² Peet³ and others. As we cannot predict with certainty the ultimate outcome of surgery in individual cases, a more accurate method of selection remains to be discovered.

The first patient was operated upon in 1931. Up to the early part of 1935, fourteen patients were submitted to operation (Group A, table 1). Group B includes those patients operated upon since the second half of 1935 and were more carefully selected. An average of 10 patients per year in Group B have had operations. We have limited our selection to patients with Grades 2 and 3 hypertension,† but with the additional requirement that they be under 40 years of age, and that there must be no evidence, or at best, slight evidence of widespread vascular disease as determined by a study of the heart, kidneys and optic disks. Furthermore, the blood pressure must fall to 150 mm systolic and 100 mm diastolic while the patient is at rest or under drug sedation. A few exceptions were made, however, especially in the matter of age, as indicated in table 1.

The first 13 patients (Group A) were subjected to a supradiaphragmatic splanchnicectomy and ganglioramisectomy, and the remainder to a two stage subdiaphragmatic or transdiaphragmatic resection of the greater and less splanchnic nerves, with the removal of the twelfth thoracic, first and second lumbar ganglia, the visualization of the adrenal glands and biopsy of each kidney. If a sufficient amount of omentum were available, the left kidney was decapsulated and a nephro-omentopexy carried out. If large accessory arteries penetrated the capsule of the kidney or the omentum was bound down by previous operative procedures, the nephropexy was not attempted.

* Received for publication December 4, 1941.

† Grading according to Keith, Wagener and Barker.⁴

- Grade 1—Mild hypertension which is normal at bed rest. Slight sclerosis of retinal vessels.
Grade 2—Moderate, fluctuant hypertension which remains above normal at rest and under sedation. Moderate sclerosis of retinal vessels.
Grade 3—Moderate to severe hypertension with little fluctuation. Sclerosis of retinal vessels with angiospastic retinitis.
Grade 4—Persistently high blood pressure. Marked sclerosis of retinal vessels with diffuse retinitis and edema of optic disks.

TABLE I
Results of Surgical Approach for Hypertension

Year		Number of Patients	Grade of Hypertension			Average Age	Operative Deaths	Postoperative				
			II	III	IV			Deaths		Blood Pressure Change		
								No of Cases	Average Duration	None	Slight	Satisfactory
1931	A	1	1	—	—	51	—	—	—	1	—	—
1934		3	1	1	1	46	—	1	6 mo	3	—	—
1935		9	2	2	5	41	—	7	20 mo	9	—	—
		2	2	1	—	31	1	—	—	—	—	1
1936		1	1	—	—	31	—	—	—	—	—	—
1937	B	9	8	1	—	35	—	0	—	3	3	3
1938		7	6	1	—	36	—	1	2 mo	4	2	1
1939		10	7	3	—	39 5 over 40	—	—	—	6	2	2
1940		12	11	1	—	34 1 over 40	1	—	—	2	3	6
Total		54	39	9	6		2	10		28	11	13

TABLE II
Blood Pressure Changes in Patients Recorded as Having a Good Response

Case	Before Operation *		After Operation †		Time since Operation
	Blood Pressure, mm		Blood Pressure, mm		
	Systolic	Diastolic	Systolic	Diastolic	
1	228	120	140	80	8 months
2	236	140	150	108	1½ years
3	190	122	146	96	3½ years
4	200	130	140	94	2½ years
5	258	140	150	100	2½ years
6	208	120	148	90	2½ years
7	220	140	140	100	2 years
8	174	110	144	90	1½ years
9	200	110	140	90	9 months
10	224	132	120	82	1 year
11	190	120	152	94	13 months
12	180	130	136	110	5 years
13	206	140	154	100	7 months

Range Systolic Diastolic Systolic Diastolic
Average 208 126 144 94 23 months

* Average of two or more readings taken at the clinic during initial examination after patient had been in recumbent position for 15 minutes

† Average of two or more monthly readings taken at the clinic after patient had been in recumbent position for 15 minutes

Two postoperative deaths (3.6 per cent) occurred. One patient died two weeks after leaving the hospital from a pulmonary embolism secondary to thrombophlebitis. The second patient had a cerebral hemorrhage 12 days after operation. Except for these two deaths the postoperative course of all the patients was without serious incident, the usual hospital stay being approximately three weeks.

We have been fortunate in being able to follow the course of all of these patients since their operation. Nine of the 13 patients in Group A seen prior to the middle of 1935 have died. Death occurred an average of 20 months after operation. One patient died four years after operation. The causes of death were related to hypertension, death being cerebral, cardiac or renal in nature. Four patients in this group are still alive at the time of writing this paper, the blood pressure remaining elevated as before operation.

There are 41 patients in Group B. Thirty-five had Grade 2 and six, Grade 3 hypertension. All but five were younger than those in Group A. Thus, five of the 10 patients operated upon in 1939 were more than 40 years

TABLE III
Blood Pressure Response in Respective Hypertensive Groups

Grade	Number of Patients	Effect of Operation on Blood Pressure	
		Slight and Considerable	No Response
1	38	21	17
2		(55%)	
3	8	3	5
4	6	(37%)	6

of age. Excluding the two postoperative deaths in Group B, only one patient has died, death took place two months after operation, of cardiac failure. Of the remaining 38 patients, 13 (34 per cent) had a satisfactory drop in blood pressure (table 2), 11 (26 per cent) had a slight drop in pressure, and 15 (39 per cent) had no change in blood pressure whatever.

In 22 cases a family history of hypertension was found, either one or both parents having an elevated blood pressure. Of these 22 patients, 10 obtained a drop in blood pressure and 12 had no drop. A family history of hypertension, therefore, is of no value in the selection or rejection of cases for operation.

The grade of hypertension played a significant rôle in the operative result, as shown in table 3. Early in our experience it was found that patients with Grade 4 hypertension did not improve following operation. The blood pressure remained at the preoperative level and death followed in the natural course of the disease. Of the patients with Grade 2 hypertension, 55 per cent of 38 obtained a drop in the blood pressure. Of those with Grade 3 hypertension, only three (37 per cent) of eight patients were benefited.

Most patients studied had Grade 2 hypertension, which accounts for the large number in this group having operation. No patient with Grade 1 hypertension was submitted to operation.

From our experience it seems certain that age is of considerable importance in selecting patients who are likely to obtain a satisfactory drop in blood pressure. Of 20 patients more than 40 years of age, only two had a drop in blood pressure. Of 32 patients less than 40, 22 (68 per cent) had a drop in blood pressure, there being 10 failures. The high percentage of

TABLE IV
Kidney Biopsies
Relationship of Kidney Disease to Drop in Blood Pressure

	Number	Number
Normal		4
Drop in blood pressure	4	
No drop in blood pressure	0	
Pathologic		21
Drop in blood pressure	11	
No drop in blood pressure	10	
Total		25

failures in 1939 when five of the 10 patients selected were more than 40 years of age is thus accounted for, whereas the larger number of successes in 1940 may be based on the fact that the patients were in the younger age group.

Symptomatic relief was found to occur in many cases even when a drop in the level of the blood pressure did not take place. This observation has been made by other investigators and is often an incentive to submit patients to operation even when a drop in the blood pressure is not likely to occur. Of 37 patients analyzed from the standpoint of symptoms, 27 had complaints related to hypertension, chiefly headache and vertigo, and of these, 20 were completely relieved of symptoms, only one half of these obtained a drop in the blood pressure. All patients having a drop in the blood pressure were relieved of hypertensive symptoms. As noted, only 27 of 37 patients had symptoms of their hypertension, almost 30 per cent of the patients were without hypertensive symptoms. These patients were studied because an elevated pressure had been found during a routine physical examination.

Of the 36 patients having only the splanchnic resection, 24 did not have a drop in the blood pressure, 12 patients obtained a drop. Of 18 patients having nephro-omentopexy in addition to splanchnic resection, 10 had a drop in blood pressure. It is not possible at this time to determine the significance of these figures as the series is not large enough. Theoretically, nephro-omentopexy is a possible means of increasing the circulation to the kidney. We have not as yet had the help of postmortem pathologic material to confirm this. Animal experimentation on this problem has given proof as to this means of increasing circulation.

In 25 patients, a specimen of the kidney was taken at the time of the operation when exploring the kidney and adrenal or when doing the nephro-omentopexy. Four patients had normal kidney tissue (table 4), all of them obtained a drop in blood pressure, three to a satisfactory level. Of the 21 patients showing various vascular and glomerular changes, there was an equal number of satisfactory and poor results. This latter finding, therefore, has no definite prognostic significance as regards a possible drop in pressure.

COMMENT

Our experience with these 54 patients confirms the experiences of others, namely that surgery of the sympathetic nervous system may have an ameliorating effect upon the blood pressure of patients with essential hypertension. The best results were obtained in patients with Grades 2 and 3 hypertension, whose ages were less than 40 and whose blood pressures responded to sedation. A better method of selecting patients for operation for hypertension needs to be devised.

Of the patients more carefully selected, 13 (34 per cent) of 38 had an excellent result and 11 had a slight drop in pressure. The blood pressure of the remaining patients was not altered. Symptomatic improvement was found to occur in 71 per cent of the patients, in one half of these the blood pressure remained elevated. This operation, we believe, is justified when patients fulfill the criteria which we have selected for the procedure, and when they understand that satisfactory lowering of the blood pressure is obtained in about one third of the cases.

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PHYSIOLOGICALLY DIRECTED THERAPY IN PNEUMONIA *

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THE use of chemotherapy has made even more important an etiological classification in the diagnosis and treatment of pneumonia. Most cases of lobar pneumonia are due to organisms whose growth is stopped by sulfathiazole or sulfadiazine, in many instances similar organisms are the cause of bronchopneumonia. However, bronchopneumonia also occurs as a primary disease, the cause of which is obscure^{1,2}. The hypothesis considered most likely in a group of cases observed at the Presbyterian Hospital in the years 1938 and 1939 was that of virus etiology³. As Kneeland pointed out in 52 carefully analyzed cases, chemotherapy had no effect on the disease, whereas supportive measures, especially inhalational therapy, were of marked value. There are other types of bronchopneumonia which occur after operations and in the course of chronic illness, such as heart disease and asthma, in which inhalational therapy may be considered of special value, since respiratory or cardiac function is frequently impaired under these circumstances.

The purpose of this communication is to point out that recent advances in physiologically directed treatment may crucially alter the course of patients with bronchopneumonia or lobar pneumonia who do not respond to chemotherapy.

METHODS

The measures employed include (1) the administration of positive pressure, (2) inhalations of helium-oxygen mixtures, and (3) inhalation of the vaporized solutions of neosynephrine and epinephrine.

Oxygen is administered under positive pressure for the treatment of edema of the lungs, either as a result of increased permeability of the capillary endothelium, as in pneumonia or irritative gas poisoning, or as a complication of heart failure⁴. The application of positive pressure to the inner surface of the lung exerts an opposing pressure on the external capillary wall, tending to prevent the exudation of serum. In addition, there is some retardation of the entrance of blood into the lungs. Because of the latter circumstance, the one contraindication to the use of positive pressure is peripheral circulatory failure, namely shock, in which the venous return to the right heart is already impaired. Positive pressure is also used in the treatment of severe cases of asthma or in cases of bronchiolitis in which there is marked narrowing of the lumen of the smaller bronchi, helium-oxygen mixtures are employed in this type of obstructive dyspnea either with or with-

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FIG 1 Oxygen meter mask with attachment to water bottle to provide pressure during expiration *

out positive pressure⁵ The most effective method of administering positive pressure is by the helium-oxygen hood in which the head of the patient is enclosed by a hood with a transparent plastocel window Pressures of 1 to 6 cm of water are maintained both in inspiration and in expiration⁶

Positive pressure may be administered in expiration only by the use of a mask in which the exhaled air passes outward through a tube which is immersed to a variable degree under water The injector mask,⁷ which may be employed both for administration of oxygen in percentages of 40 to 100

* The injector mask apparatus is made by the Oxygen Equipment Mfg Co, 405 East 62nd Street, New York, N Y

per cent and also for inhalation of helium-oxygen mixtures, may be adapted for the administration of 100 per cent oxygen under positive pressure of 1 to 5 cm. of water. In order to accomplish this the expiratory valve is removed and an adaptor containing the rubber tubing is put in its place, as shown in the accompanying illustration. Under ordinary circumstances it is generally not necessary to use pressures above 3 to 4 cm. of water. The pressure may be gradually lowered by lifting the glass connecting tube from 4 to 3 and then to 2 or 1 cm. of water as desired.

Although helium-oxygen mixtures are most effectively given by means of the hood, especially under positive pressure, the mask illustrated above may be used. It is better to admit a large flow of the helium-oxygen mixture, such as 7 to 10 liters per minute on the oxygen regulator, than to attempt to economize. In oxygen therapy the collecting bag should be kept about half expanded at the end of inspiration, but in the administration of helium-oxygen mixtures for the treatment of asthma there is even less resistance if the bag is kept almost full both during inspiration and expiration.

The inhalation of the vaporized solutions of neosynephrine and epinephrine is best obtained by passing 5 liters of oxygen from a high pressure tank through a nebulizer in which has been placed 1 cc. of a 1 per cent solution of neosynephrine and 0.5 cc. of a 1:100 epinephrine solution. Any of the nebulizers on the market may be used, the hand bulb being detached and the rubber tube from the oxygen tank being inserted in its place. Neosynephrine is used for its vasoconstriction effect on the mucous membrane of the tracheobronchial tree and 1:100 epinephrine as a bronchodilator.^{8,9}

The following case histories illustrate the type of case treated, the methods employed, and results of treatment.

CASE REPORTS

Case 1. A woman of 58 years had suffered from numerous attacks of acute bronchitis in one of which bronchial asthma had occurred. Present illness began with a cold, followed by increasing cough, dyspnea and prostration. The temperature mounted to 103° F., pulse to 120, and the respiratory rate to 28. The lungs contained sibilant râles scattered throughout the chest, moist râles at both bases, more marked on the right. The sputum revealed no pneumococci on repeated smears and cultures, nor any hemolytic streptococcus organisms. Blood count revealed 11,000 white blood cells, polymorphonuclears 75 per cent. An intermittent fever continued for two days, 101° to 103° F., preceding chilly sensations. Sulfathiazole was administered for three days, a total of 19 grams being given. At the end of this time the patient was weak and prostrated, and difficulty in breathing became pronounced. On the third day inhalations of 1.0 cc. of 1 per cent neosynephrine and 0.5 cc. of 1:100 epinephrine were begun at three hour intervals. These substances were vaporized by passing 5 liters of oxygen through a nebulizer containing the mixed solutions. Following each inhalation there was subjective relief and objective evidence of decrease in the number of sibilant râles. On the fourth day inhalations of a mixture of 25 per cent oxygen and 75 per cent helium were given for 45 minutes after each spray. The mask used was the injector meter mask which contains an inspiratory valve to prevent re-

breathing and accumulation of carbon dioxide. More marked and prolonged relief of wheezing respiration followed each helium-oxygen inhalation.

A portable roentgen-ray of the chest at home on the fourth day of disease showed nothing except increased bronchial markings. Expectoration of 120 cc of mucopurulent secretion was examined daily and showed no significant organisms, merely *Streptococcus viridans* and *N. catarrhalis* organisms. On the fifth day of disease she was put in an oxygen tent, with a transparent plexiglass canopy covering the entire bed, and an oxygen concentration of 60 per cent was maintained. Two hours later her breathing was less labored, the respiratory rate declined from 28 to 24, and she fell asleep. Although the intermittent fever continued for four more days the patient was now comfortable, with little dyspnea, prostration or weakness. After five days the tent was removed and helium-oxygen inhalations discontinued. Two days later the temperature became normal. The neosynephrine-epinephrine sprays were decreased to twice daily during the following two weeks and then stopped. Several minutes after spraying the patient generally brought up large gobs of mucus which she was previ-

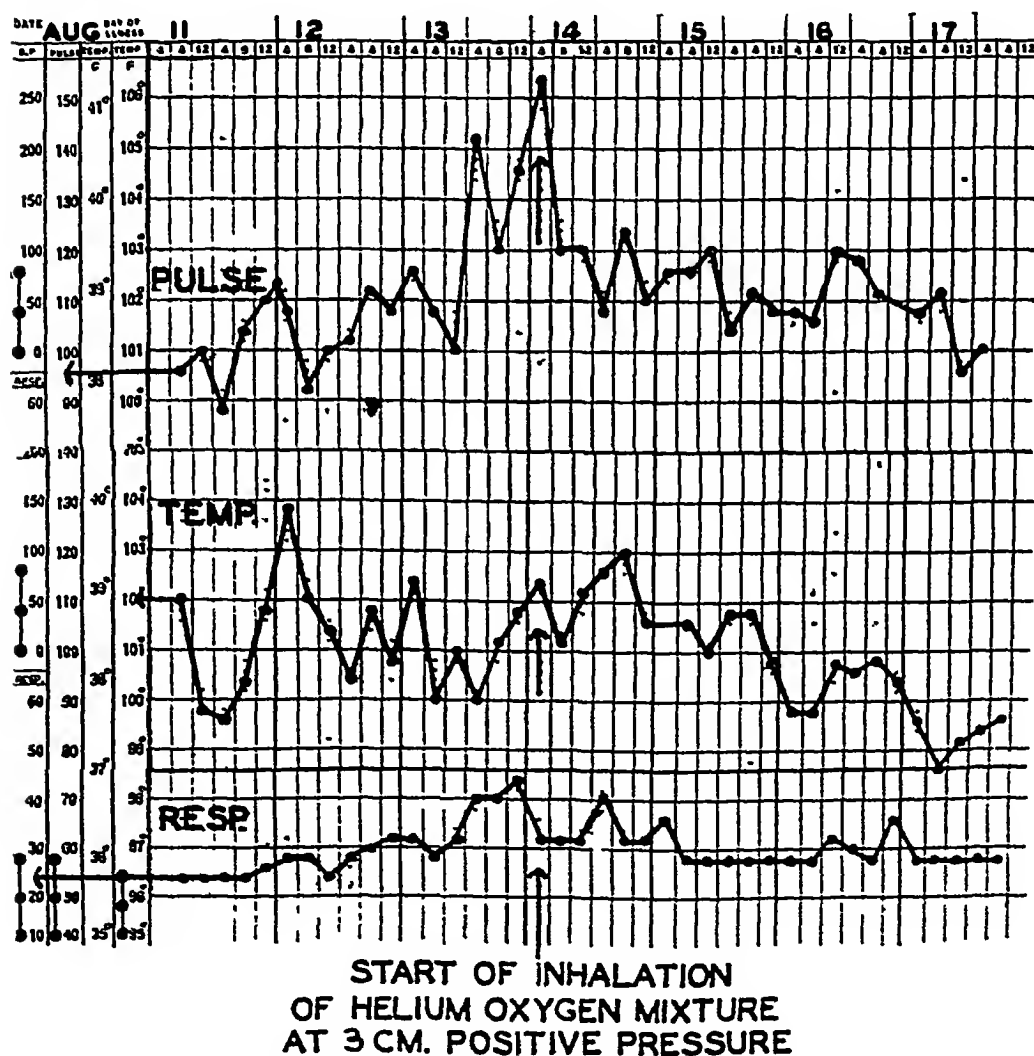


FIG 2 Effect of helium oxygen inhalation under positive pressure in a case of bronchopneumonia with pulmonary edema

ously unable to expectorate even after consciously provoked coughing. The spray appeared to facilitate expectoration of mucus which may have been adherent to the bronchial wall or caught by tight bronchial spasm.

Additional treatment consisted of ingestion of saturated solution of potassium iodide 10 c.c. four times daily, aminophylline 0.2 gm. four times daily, and codeine phosphate 0.03 gm. four times daily. On two occasions aminophylline was also given rectally for persistent bronchial spasm, 0.6 gm. in 20 c.c. of tap water, inserted by catheter and syringe, in each instance with further amelioration of bronchial spasm.

The diagnosis was bronchopneumonia of undetermined etiology, probably belonging to the group of so-called "virus" pneumonia. The inhalation of the neosynephrine-epinephrine sprays and helium with oxygen markedly reduced the severity of obstructive dyspnea and aided in expectoration of sticky mucus. Continuous residence in 60 per cent oxygen was of conspicuous and almost immediate benefit, decreasing the volume of breathing, lessening fatigue and prostration, and aiding sleep.

Case 2 Male, 30 years of age. The patient had had asthma as a child, but this had not returned in recent years. The present illness began with chilly sensations, malaise, and weakness of two days' duration, followed by a dry cough and a rise in temperature to 104° F. On examination he was found to be an acutely ill, well-developed male, in respiratory distress, the lips and nail-beds were slightly cyanotic. Over the right upper lobe a few coarse râles were heard. Blood count revealed 9,800 white blood cells, polymorphonuclears 73 per cent. The sputum showed *Streptococcus viridans* predominating on the first examination, and on the second test, a pneumococcus type 18 was isolated. He was given sulfapyridine without effect for three days. During this time he developed increasing cyanosis, dyspnea and cough, with signs of asthma which were unrelieved by hypodermic administration of adrenalin or intravenous injection of 50 per cent glucose. The roentgen-ray at this time showed consolidation in the right upper lobe and in the left upper lobe. On the seventh day after admission he was put in an oxygen tent, with a concentration of 50 per cent oxygen. Although his color was slightly improved, bronchial asthma persisted and gradually became increasingly severe. He was then placed in a helium-oxygen hood with 30 to 40 per cent oxygen, the remainder helium, under a positive pressure of 5 cm. of water.

This brought immediate and dramatic relief to the dyspnea from which he had suffered up to this time. When the pressure within the hood was lowered from 5 cm. to 3 cm., the patient immediately experienced an increasing difficulty and distress in breathing. The administration of positive pressure was obviously essential for the maintenance of comfort as well as respiratory function. For nine days he required helium-oxygen therapy under positive pressure. At the end of this time the pressure was gradually lowered and he was placed in an oxygen tent with 55 per cent oxygen. He made a slow, gradual improvement with intermittent fever over the next two weeks, and from then on gradually recovered strength.

The diagnosis was bronchopneumonia of undetermined origin, probably in the virus group. The importance of positive pressure in this case was amply demonstrated by both the subjective feeling of distress and also by the appearance of difficult breathing when it was withdrawn. Inhalational therapy enabled the patient to overcome a most severe type of obstructive dyspnea for a period of nine days. This case, as well as the succeeding one, were in the group reported by Kneeland.³

Case 3 Male, aged 29. The patient entered the hospital with a 24 hour history of cough and fever without headache or chill. On examination the lungs were clear. Temperature was 102° F. Blood count revealed 6,500 white blood cells, polymorphonuclears 69 per cent. Three days after admission he felt chilly, and his temperature rose to 104.4° F. Roentgen-ray of the chest showed a lobular pneumonia in the left lower lobe. Nine days after admission temperature was 104° F., pulse 110, respiratory rate 40. He was weak, toxic and cyanotic. He was placed in an

oxygen tent, oxygen concentration 50 per cent, and felt more comfortable until a new patch of pneumonia developed in the right lung field. Asthmatic wheezing and a constant impulse to cough added to his distress. He was now markedly dyspneic and cyanotic. The oxygen concentration was elevated to between 70 and 80 per cent, and oxygen sprays of the vaporized solutions of neosynephrine and epinephrine were given at two to three hour intervals, with marked relief. Removal from the tent atmosphere revealed the extent to which the high oxygen atmosphere was maintaining respiratory function, since severe dyspnea and cyanosis took place immediately each time he was taken out of the tent for the following four days. At that time he began to improve noticeably and oxygen therapy was stopped two days later. He made a slow gradual recovery.

The sputum culture at no time showed pneumococcus organisms. *Streptococcus viridans* predominated. Diagnosis was bronchopneumonia, probably of the interstitial or virus type, with severe diffuse involvement, profound oxygen-want, and bronchial spasm.

Case 4 A woman of 57 years became ill with cough, malaise, and intermittent fever to 102° F. On examination she was stout, moderately comfortable, with a respiratory rate of 24 and a pulse of 96. The lungs showed a few moist râles at the bases and scattered sibilant râles. During the next four days the respiratory rate gradually increased to 44, and breathing became more labored, with persistence of sibilant râles and finally the development of widespread bubbling moist râles in both lungs, heard also in the throat. Overt pulmonary edema was now present, with a pulse of 154. She was markedly dyspneic, cyanotic and in acute distress. The patient was first treated with inhalation of the vaporized spray of 15 cc of 1 per cent neosynephrine and 1 cc of 1:100 epinephrine, administering 5 liters of oxygen per minute through the nebulizer. The helium-oxygen hood was then applied with a concentration of 40 per cent oxygen and 60 per cent helium under a positive pressure of 3 cm of water.⁶ After the spray and administration of the helium-oxygen mixture under pressure the severe dyspnea was markedly relieved, the moist râles in the lungs began to clear within half an hour and were entirely absent after eight hours. As shown in the accompanying chart, the pulse rate fell the same day from 154 to 110, although the temperature still continued high at 103° F. Respiratory rate decreased from 44 to 32. For the next three days the patient was kept in the helium-oxygen hood and during this period sprays of the neosynephrine-epinephrine mixture were given at three to four hour intervals. At the end of three days she was comfortable, the helium-oxygen tent was removed, and she made an uneventful recovery.

This patient demonstrated that positive pressure is useful, not only for the maintenance of a patent airway, but also for the treatment of pulmonary edema and threatened asphyxia. The mechanism of the use of the positive pressure in the treatment of pulmonary edema has been previously described.⁴ The diagnosis was bronchopneumonia of undetermined origin, bronchial asthma, and pulmonary edema.

Case 5 The patient, a 31-year-old female, developed cough, fever, and increasing shortness of breath following a cold of one week's duration. Examination within 24 hours of onset of these symptoms disclosed beginning signs of consolidation in the left lower lobe. Temperature was 103.8° F, pulse 120, and respiratory rate 36. Examination of sputum was negative for pneumococci by the Neufeld typing method, but two cultures out of four revealed type 23 and type 30. Sulfadiazine was administered by mouth and parenterally for five and a half days, the average daily dose amounting to 5 grams. Although the temperature gradually returned to normal after four days, the patient continued to be desperately ill. On the third day of illness outspoken pulmonary edema was present, with loud bubbling râles heard in the throat and moist râles heard on auscultation throughout both chests. For a period of 36 hours repeated intravenous injections of 50 cc of 50 per cent glucose held the edema in check temporarily. On the fifth day of the disease the patient was stuporous, and

breathing was labored with a deep inspiratory retraction of the lower sternum. Moist râles were heard over both chests, front and back, and there were bubbling râles in the trachea. For three days the patient had been in an oxygen tent with a concentration of 50 per cent oxygen.

The oxygen concentration in the tent was elevated to 70 per cent for three hours by administration of 30 liters of oxygen per minute without effect on her condition. She was put in a positive pressure hood with 100 per cent oxygen and a positive pressure of 3 cm of water. Within one hour the bubbling throat râles had disappeared and no signs of moisture were heard in the left anterior chest region. There was also marked diminution of the râles in the right anterior chest. At 4 a.m. the following morning the stopper of the water bottle which regulated the pressure had slipped upward so that the patient was receiving 1 cm of water pressure. Three and a half hours later the signs of edema had returned throughout both lungs. One hour after raising the pressure to 3.5 cm both the bubbling throat râles and the moist râles over the anterior chest disappeared. The patient remained in the helium-oxygen hood for three days during which time the pressure was gradually lowered to 1 cm. During the last 24 hours she was given 70 per cent oxygen with 30 per cent helium in the hood for a total period of seven hours. She was then placed in an oxygen tent with a concentration of 70 per cent oxygen. During the next three days this was gradually lowered to 40 per cent when the tent was removed.

The day after the positive pressure treatment was begun it was found that she had consolidation of both lower lobes and the right upper lobe. On the third day after positive pressure therapy the patient ran a low fever which gradually returned to normal during the next five days.

The diagnosis was thought to be a pneumococcus lobar pneumonia, probably complicated by "virus" infection. The effect of inhalation of 100 per cent oxygen under a positive pressure of 3 to 3.5 cm of water was followed by unmistakable and prompt disappearance of the signs of widespread pulmonary edema. Other treatment included the administration of sugar and salt by Levine tube inserted through the nose, the inhalation of the vaporized sprays of 1 per cent neosynephrine and 1:100 epinephrine at three hour intervals. Neosynephrine 0.5 cc was mixed with epinephrine 0.5 cc and vaporized by running 5 liters of oxygen through a nebulizer which was held in the patient's mouth.*

The value of positive pressure in the treatment of edema of the lungs following operations is shown in an interesting report by Boothby, Mayo and Lovelace¹⁰. On the sixth day after cholecystectomy, their patient developed widespread pulmonary edema with bubbling tracheal râles which could be heard on entering the room. No reduction in the signs of edema took place on administration of 100 per cent oxygen, but 20 minutes after application of a positive pressure of 6 cm of water no râles were audible in either lung. The administration of 100 per cent oxygen was then continued, and the patient made an uneventful recovery.

DISCUSSION

Narrowing of the bronchial lumen occurs not only in asthma but is frequent in pneumonias of undetermined origin, especially in the so-called "virus" group^{1, 2, 3}. The obstruction is not only due to bronchial spasm but to edema of the bronchial wall and to accumulation of tenacious mucopurulent secretion in the small branches of the tracheobronchial tree. In-

* This case is reported through the courtesy of Dr. Russell Cecil.

halation of oxygen-enriched mixtures counteract to a variable extent impaired diffusion of oxygen and irregular ventilation of the alveoli, resulting in a decrease of the volume of breathing, lessened dyspnea and cyanosis. When the obstructive factor in dyspnea is prominent, inhalation of helium-oxygen mixtures under positive pressure decreases the mechanical effort of breathing and helps to maintain a patent airway. The application of positive pressure to the inner surface of the lung also counteracts the tendency to edema of the lungs, in lobar pneumonia as well as bronchopneumonia. Inhaling the sprays of the vaporized solutions of 1:100 epinephrine and 1 per cent neosynephrine reduces bronchial obstruction by stopping spasm of the bronchial wall, loosening tenacious mucus, and by vasoconstriction of the mucus membrane of the tracheobronchial tree.

SUMMARY

Four cases of bronchopneumonia of undetermined origin and one case of lobar pneumonia are reported in which physiologically directed therapy was of crucial value in the treatment of anoxia, respiratory obstruction and pulmonary edema. The measures employed included (1) application of positive pressure, either in conjunction with 100 per cent oxygen or helium-oxygen mixtures, (2) inhalation of the vaporized solutions of epinephrine and neosynephrine, (3) helium-oxygen inhalations, and (4) continuous administration of high oxygen concentrations in tents with completely transparent canopies. The importance of maintaining respiratory function in pneumonia unresponsive to specific drug therapy was illustrated by the response of these cases to the various technics of inhalational therapy described.

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AN OXYGEN MASK METERED FOR POSITIVE PRESSURE ¹

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IN the preceding paper ¹ the clinical advantage of breathing oxygen or oxygen-helium mixtures under positive pressure was described. When the head of the patient is placed within a hood that is made leaktight at the neck by a soft sponge rubber collar, positive pressure may be applied to the inner surface of the lung during inspiration and expiration ². Since the technical management of a hood requires more careful supervision than is ordinarily available, we have added to a mask previously described ³ a mechanism which provides positive pressure during the expiratory cycle.

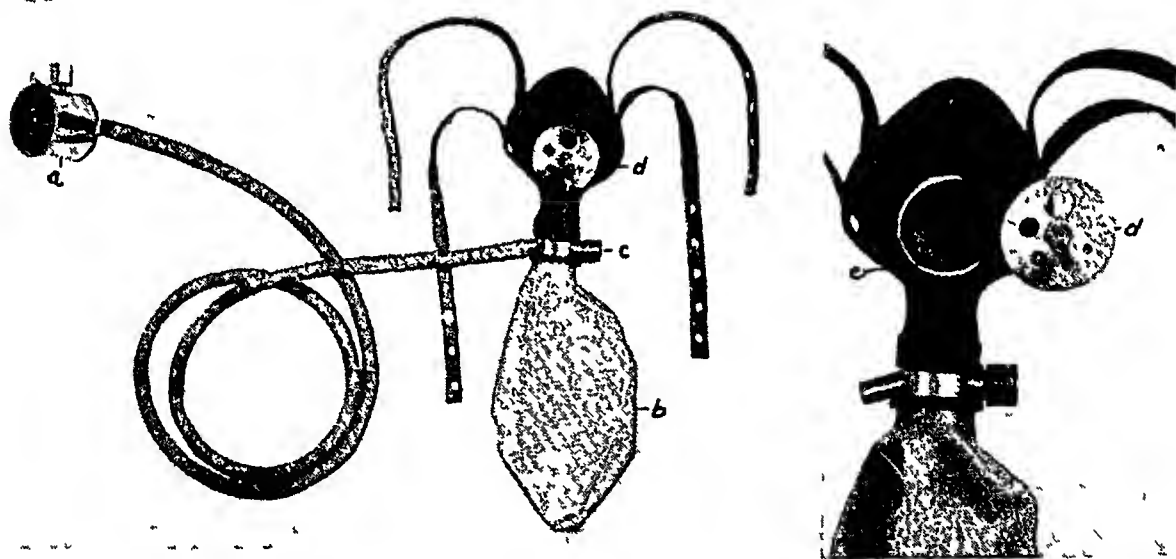


FIG 1 *a* Air mixer
 b Collecting bag
 c Emergency intake valve
 d Adjuster for control of expiratory pressure
 e Expiratory flutter valve

This consists of a series of apertures which are smaller than the diameter of the larynx. When expiration takes place through a constricted orifice, a positive pressure is reflected backward into the lung, the extent of the pressure being determined by the size of the orifice and the pulmonary ventilation. In the accompanying picture a dial is shown with five openings. When the largest opening is used there is little or no pressure during expiration. The other orifices have been calibrated during quiet breathing in an

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adult having a pulmonary ventilation of 5.5 liters per minute, so that pressures of 1, 2, 3, and 4 cm H_2O are obtained when turned to the appropriate opening. Within this dial a flutter valve is situated which prevents the outside atmosphere from entering the mask, irrespective of the size of the opening on the outside of the dial. This mask is thus metered for positive pressure.

Barach⁴ previously suggested that physiological advantages attended grunting and groaning in such instances as lobar pneumonia, bronchial asthma and pulmonary emphysema. Measurement in a tracheotomized patient of the degree of pressure developed during a forceful grunt revealed pressures as high as 30 cm H_2O . Not only does it appear likely that the expiratory grunt maintains a more patent airway, as suggested by roentgenological studies,⁵ but it also exerts an opposing force on the capillary wall which tends to stop or to reduce the passage of serum from the pulmonary capillaries into the alveoli.⁶

In this mask an injector is attached to the oxygen tank to provide a measured concentration of oxygen in the inspired air. A bag of light latex is used to collect oxygen, being separated from the mask by an inspiratory valve which prevents rebreathing. Another addition to the mask is an emergency inspiratory valve which opens when the bag is collapsed. Thus, even if a shortage of oxygen takes place for a limited period, no sensation of distress will occur since the inspiratory valve operates under minimal pressures.*

SUMMARY

A mechanism which provides positive pressure in expiration is described. By turning a dial to varying sized orifices, expiratory positive pressures may be administered from 0 to 4 cm of water. A flutter valve behind the disc makes for leaktight closure during expiration, irrespective of the size of the orifice.

Positive pressure in expiration may be used for the treatment of pulmonary edema due to increased hydrostatic pressure and anoxia, as in heart failure, or to changes in permeability of the pulmonary capillaries, as in pneumonia or gas poisoning. Positive pressure is not indicated in those conditions characterized by a deficient venous rate to the heart, such as shock.

The oxygen mask apparatus with or without positive pressure may be employed for the delivery of oxygen-enriched atmospheres from 40 to 100 per cent or for the administration of helium-oxygen mixtures. An emergency inspiratory valve has been added in order to prevent any sensation of distress if the collecting bag is temporarily collapsed.

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FUNCTIONAL MITRAL STENOSIS *

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A sign commonly considered characteristic of mitral stenosis is a mid-diastolic murmur at the cardiac apex. The murmur is usually low-pitched, rumbling, and not very loud. It is separated from the second heart sound by a definite time interval. It may be short in early diastole or may extend throughout diastole. In the latter case it decreases at first in intensity to increase again toward the end of diastole (presystolic murmur). It is usually well localized, near the apex, less commonly at the mitral valve area.

Murmurs indistinguishable from the diastolic murmur of mitral stenosis have been described in a variety of other conditions. Aortic regurgitation (Austin Flint murmur),¹ adhesive pericarditis,² various types of chronic anemia with heart enlargement,³ and rheumatic heart disease in young people without the presence of organic mitral stenosis.^{4, 5}

We have observed this murmur in young patients suffering from acute nephritis with hypertension and cardiac dilatation, disappearing when blood pressure and heart size returned to normal. Recent studies on the heart in nephritis fail to mention this murmur.⁶ We shall report these cases and attempt to find a common basis for the explanation of the diastolic murmurs occurring under different conditions.

CASE REPORTS

Case 1 A negro boy, 13 years of age, was brought to the hospital because of convulsions and generalized edema. Four weeks prior to admission he had a sore throat, followed within 24 hours by a generalized erythema. The rash and fever disappeared after a few days and at the end of the week the skin began to desquamate. Three days before admission he had a generalized convulsion. At the same time the legs and face began to swell. He became drowsy and weak. During the night preceding admission he had 9 or 10 convulsions. Physical examination showed a well developed colored boy. He was difficult to arouse and showed Cheyne-Stokes respiration. The face and lower extremities showed some edema. The skin was still desquamating. The throat and tonsils were somewhat injected and there were many sordes around the mouth. Auscultation of the lungs revealed many coarse moist rales throughout. The heart appeared somewhat enlarged, the left border of dullness extending 9 cm. from the midline in the fifth interspace. The heart sounds were distant. A rather blowing diastolic murmur was heard near the apex but was not transmitted. The heart rate was 88, respirations 24, blood pressure 170 mm. Hg systolic and 130 mm. diastolic, temperature 100. The urine showed a two plus albumin, many erythrocytes, leukocytes and granular casts. The blood showed a mild secondary anemia. A diagnosis of postscarlatinal nephritis and hypertensive encephalopathy was made.

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Treatment consisted of oral and intramuscular administration of magnesium sulphate, restriction of salt and protein but not of water. The blood pressure fell to 120 mm Hg systolic and 80 mm diastolic within six days and the cerebral symptoms disappeared. The temperature dropped to normal, the heart size decreased, and the diastolic murmur disappeared within one week after admission, although the urinary changes persisted for several months.

Case 2 This patient had been suffering from severe temporal headaches, pain across the chest and gradually increasing dyspnea following a severe sore throat. He was seen in the outpatient department four weeks after the onset of his illness. His blood pressure was found to be 180 mm Hg systolic and 120 mm diastolic. He was given digitalis. During the following two weeks the dyspnea improved but some edema of the face developed. He had a "fainting spell" three days before admission to the hospital. Following this "spell" he had complete relief from headaches.

Physical examination on admission showed a well developed negro boy, 13 years of age, in no apparent distress. There was slight edema of the face. All lymph nodes were moderately enlarged. The heart was somewhat enlarged toward both sides, M. R. being 3 cm, and M. L. 10 cm in a teleroentgenogram. There was a systolic murmur at the aortic and pulmonic areas. Both the second aortic and pulmonic sounds were markedly accentuated. There was a soft diastolic mitral murmur heard and recorded. Exercise increased the intensity of the murmur. The heart rate was 100, the blood pressure 140 mm Hg systolic and 80 mm diastolic, the respirations 20 per minute. The lungs were entirely normal. The urine was essentially normal. The blood showed a moderate anemia (red blood cells 3,900,000, hemoglobin 75 per cent). An electrocardiogram showed low T_2 and late inversion of T_3 , suggesting myocardial damage. A cold-pressor test showed a rise of blood pressure from 138 mm Hg systolic and 80 mm diastolic to 160 mm systolic and 70 mm diastolic but was essentially negative when repeated a few days later. Treatment consisted of salt free diet and continuation of digitalis, 0.1 gm daily. The patient recovered from all symptoms in the course of two weeks. The diastolic murmur disappeared. No general diagnosis was made.

Case 3 This patient was admitted to the hospital for generalized edema of three or four days' duration. Physical examination showed a well developed negro boy, six years of age, showing slight dyspnea and generalized edema. Tonsils and cervical lymph nodes were moderately enlarged. The heart was somewhat enlarged to the left, the apex extending 1 cm beyond the midclavicular line. A diastolic murmur was heard over the mitral area and demonstrated by a stethogram. The heart rate was 70 per minute, the blood pressure 150 mm. Hg systolic and 95 mm diastolic. There were signs suggestive of moderate ascites. The lungs were clear. The urine showed a moderate albuminuria, a few leukocytes per low power field, but no erythrocytes or casts. The blood showed 68 per cent hemoglobin and 3,800,000 erythrocytes. Roentgen-ray of the chest showed moderate general enlargement of the heart and slight mottling outside the cardiac area. The electrocardiogram showed a low T-wave in Lead I. Treatment consisted of bed rest and intramuscular injection of magnesium sulphate on admission. The blood pressure dropped to 118 mm Hg systolic and 70 mm diastolic on the second day, the edema disappeared within three days, the diastolic murmur was not heard after the fifth day. The urine became normal after 10 days. The child was dismissed on the twenty-third day, after another roentgen-ray showed normal heart and lungs.

Case 4 This patient, a seven year old negro boy, was brought to the hospital for edema of the face and lower extremities. Three weeks before admission he contracted a severe cold and sore throat, but recovered completely within a few days. Four days before admission he injured his left thumb and contracted a superficial skin infection. On the following day the scrotum began to swell and one day later the mother noticed

edema of the face which increased in intensity until admission. Physical examination showed a well developed boy with moderate edema of the face, anterior abdomen, genitalia, and thighs. The heart showed definite enlargement, the left border extending 2 cm beyond the midclavicular line. There was a rough systolic murmur heard loudest over the mitral area and transmitted to the axilla. In addition, there was a low pitched short diastolic murmur, not transmitted, heard best midway between the mitral area and the apex (figure 1a). The heart rate was 108 per minute, the blood

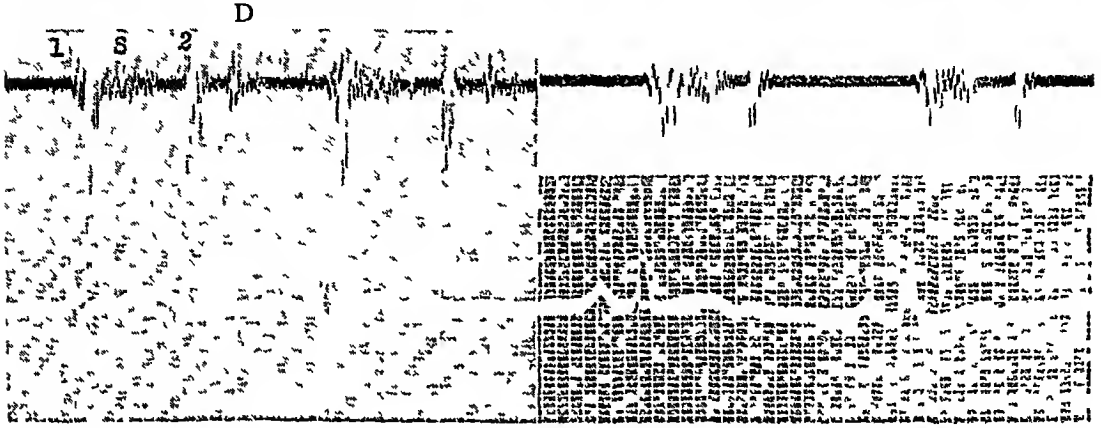


FIG 1a 1—first heart sound, S—systolic murmur, 2—second heart sound, D—diastolic murmur

FIG 1b Note absence of diastolic murmur

pressure 160 mm Hg systolic and 120 mm diastolic. The urine was free of albumin on admission, but showed small amounts during the following three days. Examination of the blood showed leukocytes 20,000, erythrocytes 3,310,000, hemoglobin 8.4 grams. An electrocardiogram, taken two days after admission, suggested slight myocardial damage because of low T, "W" shaped QRS, and late inversion of T.

A tentative diagnosis of acute glomerulonephritis was made. Within four days the skin infection healed under surgical treatment. The edema disappeared, the urine became free of albumin, the blood pressure dropped to 98 mm Hg systolic and 48 mm diastolic, and the diastolic murmur could neither be heard nor demonstrated in a stethogram (figure 1b). The patient was dismissed free of symptoms on the sixth day.

DISCUSSION

These four patients have several points in common. All four of them were young male negroes who gave a history of past good health and, notably, of absence of rheumatic heart disease, all four suffered more or less from acute hypertension and consequent cardiac dilatation, all four showed moderate anemia, and in all four cases rheumatic heart disease was suspected at some time during hospitalization.

The condition does not appear to be uncommon. These cases were observed during a period in which approximately 10 other cases of acute nephritis were seen in the hospital. These other cases did not show the diastolic murmur, although some of them did show signs of cardiac failure and dilatation.

The origin of the diastolic murmur may be tentatively explained as follows:

The formation of eddies in the flow of liquids through tubes is favored by increased velocity of flow, rapid change in diameter of the tube (diverging boundaries) and decreased viscosity of the liquid. The eddies produce vibrations which may be heard as murmurs. It is not known at present whether the valve cusps, chordae tendineae, papillary muscles or extracardiac structures contribute most to the vibrations. Conditions in mitral stenosis are favorable for the production of murmurs. Auricular pressure is high and the velocity of blood flow, even if the volume flow is decreased, is therefore rapid, the mitral orifice is narrowed, whereas the auricle, and sometimes the ventricle also, is dilated, and, finally, anemia is frequently present reducing the viscosity of the blood. Flow from the auricle into the ventricle is not uniform as may be seen from ventricular volume curves.⁷ Flow is rapid in early diastole immediately after the opening of the A-V valves. The intensity of the murmur diminishes when auricular pressure decreases during the course of diastole and may again increase preceding systole when auricular contraction increases auricular tension.

Our patients presumably had dilated auricles and ventricles, the viscosity of their blood was decreased because of anemia, and their auricular pressures were high because of beginning heart failure. The mitral orifice in acute hypertension and in the other above named conditions is probably of normal size. However, it is possible as suggested previously⁴ that the change in diameter of the tube is more important than the actual size of the opening. Murmurs are absent in small infants although the valve orifice is smaller than in most adults suffering from mitral stenosis. Murmurs may also be absent in pulmonary stenosis when the pulmonary artery is hypoplastic but, on the other hand, murmurs may be heard over aneurysms in the absence of any obstruction.

SUMMARY

A mid-diastolic apical murmur was heard and recorded in four cases of acute transient hypertension in negro boys.

The possibility of an erroneous diagnosis of mitral stenosis in this condition has been pointed out.

An attempt has been made to explain the occurrence of the murmurs in different conditions by analyzing the hydrodynamics of flow through the mitral orifice, the major factor being the relatively small mitral orifice between acutely dilated auricle and ventricle.

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THE ASSOCIATION OF ATROPHIC GASTRITIS WITH HYPOTHYROIDISM; A PRELIMINARY REPORT OF 11 CASES¹

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It is well recognized that anemia and hypochlorhydria or achlorhydria are frequently present in patients having hypothyroidism or myxedema¹ Gastroscopy has demonstrated that atrophy of the gastric mucosa is also frequently associated with anemia and hypochlorhydria or achlorhydria²

This frequent occurrence of anemia and hypochlorhydria or achlorhydria in both hypothyroidism and atrophic gastritis led me to believe that it would be worth while to study a series of hypothyroid or myxedematous patients to determine whether or not there is a significantly high percentage of gastric atrophy present in these conditions

Herein are reported a series of 11 cases of hypothyroidism and myxedema examined at the Colorado General Hospital and associated Out-Patient Clinic, in which examination of the stomach has been made gastroscopically or microscopically

To save time and space, only data which seem significant to this study will be presented, and non-related findings, both positive and negative, will be omitted as far as possible

CASE REPORTS

Case 1 L L, female, aged 28, entered the Medical Clinic September 8, 1939 with a multitude of complaints, among which were nervousness for six months, several menstrual periods each month for the past six months, numbness of the extremities irregularly for several months, anorexia, nausea and "gas" on the stomach, occasional vomiting, abdominal pains, and constipation all her life There had been no weight loss The onset of most of these symptoms occurred after the death of her mother, upon whom she was excessively dependent An operation for chronic appendicitis was performed in 1934, and in 1935 for adhesions The medical and gynecological examinations revealed no definite abnormalities Pulse was 76, regular Blood pressure was 106 mm Hg systolic and 66 mm diastolic Provisional diagnoses of psychoneurosis and functional uterine bleeding were made

Laboratory examination Blood count hemoglobin 12.5 gm, red blood cells 4,250,000 per cu mm, white blood cells 6,000 per cu mm, polymorphonuclears 54 per cent, lymphocytes 32 per cent, endothelial cells 2 per cent, and eosinophiles 12 per cent Gastric analysis showed no free hydrochloric acid in either fasting specimen or after the feeding of alcohol With histamine, the free hydrochloric acid was 16° and the total acidity from 13° to 60° Basal metabolic rate was minus 29 The gastrointestinal roentgen-ray series indicated a constant deformity of the duodenal bulb suggesting ulceration Gall-bladder visualization showed a slight sluggishness in function Gastroscopic examination revealed a patchy atrophic gastritis of the body of the stomach

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Case 2 A B, female, aged 63, entered the Medical Clinic September 29, 1939, complaining of chills (apparently the sensation of coldness rather than a true chill), weakness and joint pains of three years' duration. In the system review, history of nausea and occasional vomiting was elicited. She had swelling of the ankles also. On physical examination, her skin was dry and pale, pulse 66, blood pressure 128 mm Hg systolic and 80 mm diastolic. Provisional diagnosis: Osteo-arthritis, hypothyroidism and atrophic gastritis.

Laboratory examination: Blood count: hemoglobin 120 gm, red blood cells 3,800,000 per cu mm, white blood cells 6,600 per cu mm, and normal differential count. Basal metabolic rate was minus 24. Gastric analysis showed achlorhydria on fasting and after alcohol, total acidity 19° to 42°. Gastrointestinal roentgen-ray series showed some deformity in the pyloro-duodenal region, probably due to an organic lesion, but no evidence of six hour residue. Gastrosopic examination made November 8, 1939 showed extensive atrophic gastritis of the body of the stomach, slight superficial gastritis, and one superficial erosion.

Case 3 M B, female, aged 44, entered the Medical Clinic September 19, 1939, complaining of poor vision of the right eye, tremor (both of these due to a neurological abnormality which improved rapidly without any treatment other than thyroid), puffiness of the eyes, dyspnea and swelling of the ankles. She also noted that her speech had slowed considerably. She had a good appetite, no nausea or vomiting, was constipated, but had no abdominal pain. She was gaining in weight. She had irregular menstruation, one miscarriage, but no other pregnancies. The physical examination showed a three plus puffiness beneath the eyes. The skin of the face was pasty in appearance, dry and scaly over the body. There were supraclavicular pads of fat, palpable liver edge, and the ankle jerks showed delayed and prolonged decontraction phase. Provisional diagnosis (exclusive of neurological disease) Myxedema.

Laboratory examination: Basal metabolic rate was minus 48. Blood count: hemoglobin 140 gm, 4,270,000 red blood cells, 6,350 white blood cells, and normal differential count. Gastric analysis showed 24° to 36° free hydrochloric acid and 50° to 86° total acidity. The gastrosopic examination, November 17, 1940, showed small but definite areas of atrophic gastritis.

The patient's basal metabolic rate was brought up to plus 3 by December 11, 1939 under 2 grains of thyroid extract daily. She lived out of the city, and returned to her home at this time on this dosage of thyroid. On August 19, 1940, she returned to the clinic for a check examination. She was feeling well. Basal metabolic rate was minus 18, and the blood count showed 11 gm hemoglobin, 4,400,000 red blood cells, and 7,500 white blood cells. Gastric analysis (fasting specimen only) showed 22° free hydrochloric acid and 43° total acidity. The gastrosopic examination showed slightly more extensive atrophic gastritis than at the original examination.

Case 4 E P, female, aged 18, was first seen in the Medical Clinic August 4, 1937, having been referred by the obstetrical department. A severe anemia, hemoglobin of 9.3 gm, 2,940,000 red blood cells, 7,050 white blood cells, and a normal differential count were found. She responded moderately well to iron and liver (orally and intramuscularly). She returned September 17, 1937 after her delivery and was found to be moderately anemic, but she discontinued treatment after two months. She reentered the clinic September 21, 1938 complaining of loss of weight, and in addition she was again found to be anemic. Treatment, consisting of iron, dilute hydrochloric acid and oral liver, resulted in only partial improvement of her anemia so liver extract intramuscularly was begun. The patient again discontinued treatment. On November 1, 1939, she returned complaining of dyspnea and of being underweight. Complete examination was done and a slightly hyperchromic type of anemia found. Gastric analysis showed 0° to 48° free hydrochloric acid, and 12° to 59° total acidity. Basal metabolic rate was minus 19. Because of the persistent anemia gastrosopic

examination was done November 27, 1939 and an extreme atrophic gastritis of the body of the stomach was found

Case 5 G R, female, aged 33, entered the Medical Clinic September 6, 1939, complaining of general run-down condition, fatigue, nausea, vomiting, choking sensation (attributed by the patient to a goiter), pain in the lower right quadrant, and cough. System review elicited the history of "canker" sores in the mouth, anorexia, flatulency, loss of 12 pounds in weight. There had been an appendectomy at 18. Physical examination showed no goiter, pulse 80, regular, blood pressure 140 mm Hg systolic and 90 mm diastolic, tenderness over the cecum and sigmoid colon. Provisional diagnosis of anxiety state, irritable colon and chronic bronchitis was made.

Laboratory examination. Blood count hemoglobin 150 gm, red blood cells 3,750,000, white blood cells 6,500 and a normal differential count. Gastric analysis showed 12° free hydrochloric acid and 43° total acidity. Basal metabolic rate was minus 23. The gastroscopic examination made on December 4, 1939 showed patchy atrophic gastritis of the body of the stomach and slight superficial gastritis near the cardia.

Case 6 T D, female, aged 45, entered the Medical Clinic September 12, 1939 with the history of having had pernicious anemia for nine years, complaining at this time of excessive bleeding following the extractions of teeth, and weakness. System review elicited swelling of the face and body at times, chilly sensation almost constantly, good appetite but soreness and bloating in the abdomen, constipation, frequent watery stools. Physical examination showed a pale icteric appearance, and a dry and scaly skin. Pulse 65, regular, blood pressure 110 mm Hg systolic and 70 mm diastolic. There was a systolic murmur at the apex. Provisional diagnosis of pernicious anemia was made.

Laboratory examination. Blood count hemoglobin 133 gm, red blood cells 3,250,000, white blood cells 4,600, and a normal differential. Prothrombin time was normal. Gastric analysis showed achlorhydria after histamine injection, with total acidity 16°, and three plus blood. Basal metabolic rate was minus 26. Blood cholesterol 230 mg. The gastroscopic examination on January 31, 1940 showed patchy atrophy of the stomach, many hemorrhages in the mucosa and three small polyps.

Case 7 E L, female, aged 61, entered the Colorado General Hospital February 5, 1940. History obtained from the patient's daughter stated the patient had not been well for 25 years, gradually becoming weaker until she had been confined to bed and entirely helpless for the past month. She had had severe constipation, and for one month an abdominal ache which was relieved by the passage of flatus. She had been cold all her life, and had had scaly skin, dyspnea and edema for years. The physical examination showed a cold, dry scaly, pale skin, thick lips, eyes nearly swollen shut, pulse 60, regular, blood pressure 120 mm Hg systolic and 80 mm diastolic, distended abdomen, edema of the extremities. Reflexes showed delayed contraction and relaxation. The provisional diagnoses of myxedema, avitaminosis, and gastrointestinal disease were made.

Laboratory examination. Blood count 95 gm hemoglobin, 2,590,000 red blood cells, 2,400 white blood cells, and a normal differential count. Slight variation in size and shape of the red cells was noted. Basal metabolic rate was minus 41. The gastric analysis showed no free hydrochloric acid and not over 16° total acidity with histamine. The roentgen-ray showed enlargement of the heart. The electrocardiogram gave a typical myxedema picture. On March 4, 1940, the patient died. Postmortem examination was performed and the following diagnoses made: Severe hypothyroidism with myxedema, cardiac hypertrophy, bronchopneumonia, severe gastric atrophy, cause undetermined.

Microscopic examination of the stomach. "The mucosa is thin and acellular, revealing moderate capillary congestion. The gastric glands are decreased in number

and size, revealing distortion and shiveling. Slight exfoliation of the superficial epithelium is seen in some parts. The muscularis mucosa is thin but well defined."

Case 8 J W, female, aged 53, an old patient in the clinic returned March 13, 1940 because of pain in the left lower chest and upper left abdomen anteriorly. On previous admissions the patient had had roentgen-ray evidence of gall-bladder disease and basal metabolic rate as low as minus 30. The physical examination showed no abnormality except moderate obesity. Pulse was 80, blood pressure was 132 mm Hg systolic and 88 mm diastolic.

Laboratory examination. Blood count 150 gm hemoglobin, 4,500,000 red blood cells, 7,700 white blood cells, and normal differential count. Gastric analysis showed 29° free hydrochloric acid, total acidity 36°. Basal metabolic rate was minus 24. Roentgen-ray of the gall-bladder showed delayed emptying. Gastroscopic examination July 27, 1940 revealed hemorrhagic atrophic gastritis of the cardiac end of the stomach. The second gastroscopic examination September 23, 1940, after two months of treatment, showed atrophic gastritis but no hemorrhages.

Case 9 I L, female, aged 66, entered the Medical Clinic July 8, 1940, complaining of difficulty in walking straight, exhaustion and swelling of the eyes, since the fall of 1937. There were no definite abdominal symptoms. The patient had dyspnea and palpitation upon exertion. Physical examination showed a pale, dry skin, and marked supraclavicular pads of fat. Pulse 57, blood pressure 126 mm Hg systolic and 76 mm diastolic. Provisional diagnoses of cerebral arteriosclerosis, hypothyroidism and anemia were made. Blood count showed hemoglobin 12.5 gm, red blood cells 3,900,000, white blood cells 5,450 and normal differential count except for 8 per cent eosinophiles. Basal metabolic rate was minus 48, blood cholesterol 296 mg. Gastric analysis showed no free hydrochloric acid, 24° total acidity. Gastroscopic examination made July 30, 1940 showed atrophic gastritis with one hemorrhagic area visualized.

Case 10 B M, female, aged 47, entered the Medical Clinic March 25, 1940 complaining of fatigue and weakness, pain in the back and shoulders, premenstrual pain, and irregular and excessive menstrual flow. Onset of symptoms was six years prior to admission, following a thyroidectomy (pre-operative diagnosis of hyperthyroidism). System review elicited the complaints of dryness of hair and skin, constant "chilliness," and slowing of speech and thinking. Physical examination showed a dry and scaly skin, swollen eyelids and lips, sparsity of hair and eyebrows, slowing of speech. Pulse 60, blood pressure 155 mm Hg systolic and 105 mm diastolic. Provisional diagnosis of postoperative myxedema was made. Basal metabolic rate was minus 36. Blood cholesterol was 272 mg. Blood count hemoglobin 13.0 gm, 4,700,000 red blood cells, 6,600 white blood cells, and a normal differential. The patient was started on thyroid treatment, but discontinued coming to the clinic after two months. On August 7, 1940 she returned to the clinic, at which time the blood count showed 9.8 gm hemoglobin, 3,150,000 red blood cells, 6,500 white blood cells. Gastric analysis showed the presence of free hydrochloric acid, quantitative analysis was not done. The gastroscopic examination was done September 13, 1940 and erosive atrophic gastritis of the body of the stomach was found.

Case 11 H C, female, aged 49, entered the Medical Clinic July 17, 1940 complaining of pain and stiffness of the joints of her fingers and toes for the past year, nervousness the past few years, belching and occasional vomiting the past year, and constipation. Physical examination showed no abnormality except tenderness and swelling of the small joints of the hands and feet. Pulse was 64, regular, blood pressure 154 mm Hg systolic and 100 mm diastolic. Blood count showed 13.3 gm hemoglobin, 3,900,000 red cells, 6,600 white blood cells, large number of lymphocytes (60 per cent). The gastric analysis showed 0° to 3° free hydrochloric acid and 5° to 20° total acidity. Basal metabolic rate was minus 23. Blood uric acid was 4.6 mg per 100

c c The gastroscopic examination was done September 17, 1940 and diagnosis of mild superficial and probable atrophic gastritis was made

Before discussing these cases, it will be of value to tabulate the findings as to the severity of the hypothyroidism (as evidenced by the basal metabolic rate and the presence of myxedema), the blood findings, gastric acidity and the presence or absence of digestive or gastrointestinal complaints

Case	B M R	Myxedema	Anemia	Gastric Acidity	Gastro-intestinal Symptoms
1	Minus 29	+	+	Low	+
2	Minus 24		+	Achlorhydria	+
3	Minus 48		0	Normal	0
4	Minus 19		+	Normal	0
5	Minus 23	+	+	Low	+
6	Minus 26		+	Achlorhydria	+
7	Minus 41		+	Low	+
8	Minus 24		0	Low	+
9	Minus 48	+	+	Achlorhydria	0
10	Minus 36	+	+	Present (quantity not determined)	0
11	Minus 23		+	Low	+

Arranged as to myxedematous cases and simple hypothyroidism cases

Myxedema	Anemia	Acidity	Gastrointestinal Complaints
1	0	Normal	0
2	+	Low	+
3	+	Achlorhydria	0
4	+	Present (quantity not determined)	0
Hypothyroidism	Anemia	Acidity	Gastrointestinal Complaints
1	+	Low	+
2	+	Absent	+
3	+	Normal	0
4	+	Low	+
5	+	Absent	+
6	0	Normal	+
7	+	Low	+

Eleven cases are too small a series from which to draw too definite conclusions in regard to the incidence of gastric atrophy in hypothyroidism, but the high correlation found in this group of patients is significant enough to justify publication of this preliminary report in the hope that it will stimulate other observers to look for this correlation in the cases which come under their observation. The number of cases of hypothyroidism or myxedema in which examination of the gastric mucosa can be made will not be large in the average clinic, and it probably will take considerable time before sufficient cases have been observed to determine accurately how high is the correlation between hypothyroidism and gastric atrophy

The diagnosis of atrophy of the gastric mucosa made gastroscopically has many pitfalls since it depends usually upon a brief inspection of the gastric mucosa by a single observer, but in this work I have attempted to prevent this tendency to subjective error by having my observations checked in as many cases as possible by one or two other observers, and in cases 3 and 8 the patients were examined on two different occasions. The most convincing evidence, however, is the data obtained from case 7, in which the atrophy of the gastric mucosa was proved microscopically.

The possibility that the gastric atrophy might be due to an independent coincidental disease of the gastrointestinal tract rather than hypothyroidism was considered, especially as two-thirds of these cases had gastrointestinal symptoms. However, of the more definite cases, the four true myxedemas, three had no gastrointestinal symptoms and the fourth had only slight gastrointestinal complaints, so I believe this possibility is untenable.

With regard to the high incidence of digestive complaints in these cases, the report of Bassler³ is of great interest. "Masked hypothyroidism may be the underlying cause of serious gastrointestinal disturbances and may imitate symptoms of chronic involvement of abdominal structures." "The gastrointestinal symptoms as arrayed by Ramsey are anorexia, flatulence (especially after meals), constipation, occasional nausea and rare vomiting, gastric hypoacidity and achlorhydria, and abdominal pains which may simulate gastro-duodenal ulcer, cholecystitis and appendicitis." The symptoms described above are consistent with those of atrophic gastritis,² and the supposition that such atrophy does exist in this type of case would do much to explain the underlying mechanism of such gastrointestinal symptoms as observed by Bassler.

These cases have also been examined with the fact in mind that anemia does at times alter the basal metabolic rate.⁴ This effect varies, at times raising the rate, at times lowering it. However, the average basal metabolic rate of those cases in this series having anemia is minus 30, which is more than would be expected from anemia alone, and of the total series, two of the cases did not show any anemia.

Speculation as to why gastric atrophy should occur with hypothyroidism suggests various possibilities. The most simple explanation would seem to be that the slowing up of metabolic processes occurring in hypothyroidism reflects itself by decreased activity and replacement of cells of the gastric glands,⁵ and that the gastric atrophy is a direct result of the hypothyroidism. The anemia which is found so frequently in hypothyroidism could, by this hypothesis, be explained in two ways: first, on the basis of decreased activity of the blood forming tissues, as the direct result of inadequate stimulation by the thyroid gland, secondly, the anemia might be secondary to the gastric atrophy, which in itself predisposes to anemia, rather than due directly to thyroid deficiency.

Mansfield⁶ has produced evidence for the existence of a myelotropic hormone derived from the thyroid and found in fresh thyroid tissue but

not present in desiccated thyroid or thyroxine. In view of this work, it seems possible that it is the lack of a specific myelotropic hormone of the thyroid in some or all cases of hypothyroidism rather than a non-specific depression of metabolism which accounts for the anemia present so frequently in these cases.

With the ever increasing number of hormonal substances being discovered, I believe it is not unlikely that the atrophy of the gastric mucosa may also be due to a deficiency of a specific "gastrotropic hormone" rather than to a non-specific effect of thyroid deficiency.

Case 3 seems to favor the theory that the anemia and the atrophy of the stomach are not due entirely to the thyroxine deficiency, for when this case was observed for the second time after eight months of fairly adequate thyroid therapy, it showed even more extensive atrophy of the stomach than at the first examination and for the first time showed a lowered hemoglobin.

If such a gastrotropic hormone should be found to exist, it should open up a promising new approach to the search for the still unknown basic cause of anemias associated with gastric atrophy (both macrocytic and hypochromic types), and combined cord degeneration. Perhaps the relationship of atrophy of the stomach to hypothyroidism may furnish a clue to the discovery of such a hormone.

SUMMARY

Gastroscopic (and in one case, microscopic) examinations have been made of the gastric mucosa in a series of 11 cases of hypothyroidism and myxedema.

Atrophy of the gastric mucosa was diagnosed positively in 10 cases, probable atrophy was diagnosed in the eleventh case. No definite conclusions can be drawn from such a small series, but the hypothesis that hypothyroidism and myxedema are accompanied by a high incidence of gastric atrophy seems worth further investigation.

The possibilities have been suggested that the gastric atrophy and anemia may be a direct result of hypothyroidism, or that there may be, in cases of hypothyroidism, an associated deficiency of myelotropic hormone⁶ and a deficiency of a postulated "gastrotropic hormone" to account for the anemia and gastric atrophy.

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PARENTERAL USE OF THE SULFONAMIDES

A CLINICAL AND EXPERIMENTAL STUDY*

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THE efficacy of the sulfonamide drugs in the treatment of many infections is generally accepted. The Council on Pharmacy and Chemistry has listed certain sulfonamides, stating their action, use, toxicity, and general status. It must be emphasized, however, that these chemicals are still relatively new and, therefore, require further experimental study in some phases of their behavior. At present in the United States, oral or intravenous administration is favored, although in England^{1,2} and Canada³ the intramuscular route is also used. We have studied the rapidity of absorption and secretion of the sulfonamide drugs, the degree of acetylation, and toxic effects, both general and local. Our observations indicate that different patterns of effect are produced by different routes of administration. This article presents a comparative study of different routes of administration and discusses the therapeutic advantages and safety of the intramuscular route.

PROCEDURE

The following observations were made on six groups of average hospital patients, as well as on three normal healthy volunteers who took all six tests. Some of the subjects had mild infections at the time, others were convalescent, most of them were ambulatory. None had fever, and none of the subjects had received sulfonamide therapy for at least a week previous to the experiment. All subjects were on a regular house diet, and fluids were allowed as desired.

In the first group each subject received a single dose of two grams of sulfapyridine by mouth, in the second two grams of sodium sulfapyridine intravenously, in the third two grams of sodium sulfapyridine intramuscularly. Those of the fourth group received two grams of sulfathiazole orally, the fifth group two grams of sodium sulfathiazole intravenously, and the sixth group two grams of sodium sulfathiazole intramuscularly. The intravenous doses were given as a 5 per cent solution of the drug in distilled water, and the intramuscular doses were given as a 33 1/3 per cent solution. The intramuscular dose was given deeply into the gluteal muscles as a single injection of 6 c c of the solution.

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Blood levels were determined at frequent intervals throughout the following 24 hours, and the total urinary excretion of the drug for 24 hours was observed. Free and conjugated drug in the blood and urine were determined by the Marshall-Litchfield method, using the Cenco Photometer with a Wratten No 74 green filter.

Separate groups of subjects were used for each procedure, but since the curves of the three volunteers who went through the entire series fell into the same general pattern as did the others, we feel that the heterogeneity of the groups does not appreciably affect our results.

RESULTS

Tables 1 and 2 summarize the data concerning blood levels, giving the average figure for each group as well as the range of individual readings. Curves of the average blood concentrations for each group are shown in figure 1.

There was considerable variation among individuals, even upon intravenous administration. In one subject the maximum blood concentration following an oral dose of sulfapyridine was not reached until the eighth hour, whereas the average peak for the group occurred at four hours. The narrowest range and, therefore, the most consistent results among individual subjects occurred with intravenous sodium sulfapyridine.

Maximum concentration in the blood was reached in two to four hours after oral and intramuscular medication. Intravenous injection brought an immediate high concentration, which fell rapidly to a level below oral and

TABLE I
Blood Concentration in Milligrams Per Cent Following the Administration
of Two Grams of Sulfapyridine

	Time	Average of Group		Individual Range	
		Free	Total	Free	Total
Oral 7 Subjects	2 hr	1.7	1.9	0.6-3.1	0.7-3.1
	4	2.3	3.0	1.5-3.4	1.9-3.7
	6	1.5	2.5	1.0-1.9	2.1-3.3
	8	1.4	2.4	0.8-2.3	1.9-2.9
	10	1.4	2.2	0.6-2.0	1.7-2.8
	24	0.6	0.9	0.2-1.1	0.5-1.3
Intramuscular 11 Subjects	1 hr	1.4	1.5	0.4-1.6	0.6-2.5
	3	2.2	2.8	1.5-3.4	2.0-3.5
	5	2.1	3.0	1.2-3.6	1.8-4.0
	7	1.8	2.5	0.9-3.3	1.7-3.5
	24	0.4	0.8	0.2-0.8	0.4-1.1
Intravenous 5 Subjects	5 min	5.4	5.5	3.4-8.7	3.5-8.7
	1 hr	3.0	3.5	2.0-4.0	2.4-4.4
	2	2.4	3.2	1.9-3.2	2.4-4.2
	4	1.7	2.5	1.6-1.8	1.7-3.7
	8	1.1	2.0	0.8-1.3	1.5-2.4
	24	0.4	0.9	0.1-1.0	0.2-1.6

TABLE II
Blood Concentration in Milligrams Per Cent Following the Administration
of Two Grams of Sulfathiazole

	Time	Average of Group		Individual Range	
		Free	Total	Free	Total
Oral	1 hr	2.2	2.3	1.2-2.7	1.3-2.7
	2	2.6	2.7	2.4-3.0	2.5-3.1
	4	2.6	3.1	1.4-4.0	1.8-4.6
4 Subjects	6	2.2	2.7	1.0-3.6	1.5-4.3
	8	1.6	1.9	0.8-2.6	0.9-3.1
	24	0.3	0.6	0.2-0.4	0.2-1.8
Intramuscular	1 hr	1.3	1.5	0.3-2.0	0.5-2.2
	3	2.5	2.8	1.8-3.1	2.4-3.3
	5	2.5	2.9	1.7-3.3	2.7-3.3
7 Subjects	7	2.3	2.7	1.7-2.5	2.0-3.1
	9	1.9	2.1	1.3-2.3	1.7-2.4
	24	0.5	0.6	0.3-0.7	0.4-0.8
Intravenous	1 hr	5.1	5.4	3.0-9.0	3.0-9.0
	2	3.7	3.8	2.3-6.2	2.4-6.4
7 Subjects	3	3.4	3.7	2.0-5.5	2.3-6.0
	5	2.3	2.6	1.5-4.0	1.6-4.4
	24	0.2	0.3	0.2-0.4	0.2-0.4

intramuscular readings within three or four hours. The intramuscular route produced approximately the same maximum level as that attained by oral administration, absorption was slightly slower, however, and an effective blood level was maintained for a longer period of time. Sulfathiazole, by all three methods, gave a higher peak than the same dose of sulfapyridine, and the rate of absorption was more rapid. Maximum blood concentrations of sulfathiazole were maintained somewhat longer than those of sulfapyri-

TABLE III
Percentage Excretion in the Urine for First 24 Hours Following the Administration
of Two Grams of the Drug

	Sulfapyridine			Sulfathiazole	
	Average	Range		Average	Range
Oral	48	30-75	Oral	78	68-90
Intramuscular	50	38-75	Intramuscular	68	55-85
Intravenous	40	25-85	Intravenous	87	79-96

dine, producing a flat peak followed by a plateau, in contrast with the sharp peak of the sulfapyridine curve. This was true of both oral and intramuscular methods of administration. The blood concentrations at the end of 24 hours were approximately the same for all three methods.

The degree of acetylation was considerably greater after sulfapyridine than after sulfathiazole. With both drugs the percentage of the conjugated form in the blood after a single dose rose to a maximum at six to seven hours.

and then fell steadily. The degree of acetylation was roughly the same by all three methods.

Table 3 shows the percentage of drug recovered from the urine in 24 hours. There was great variation among individuals, although the relative amount of sulfathiazole recovered was consistently much greater than of sulfapyridine.

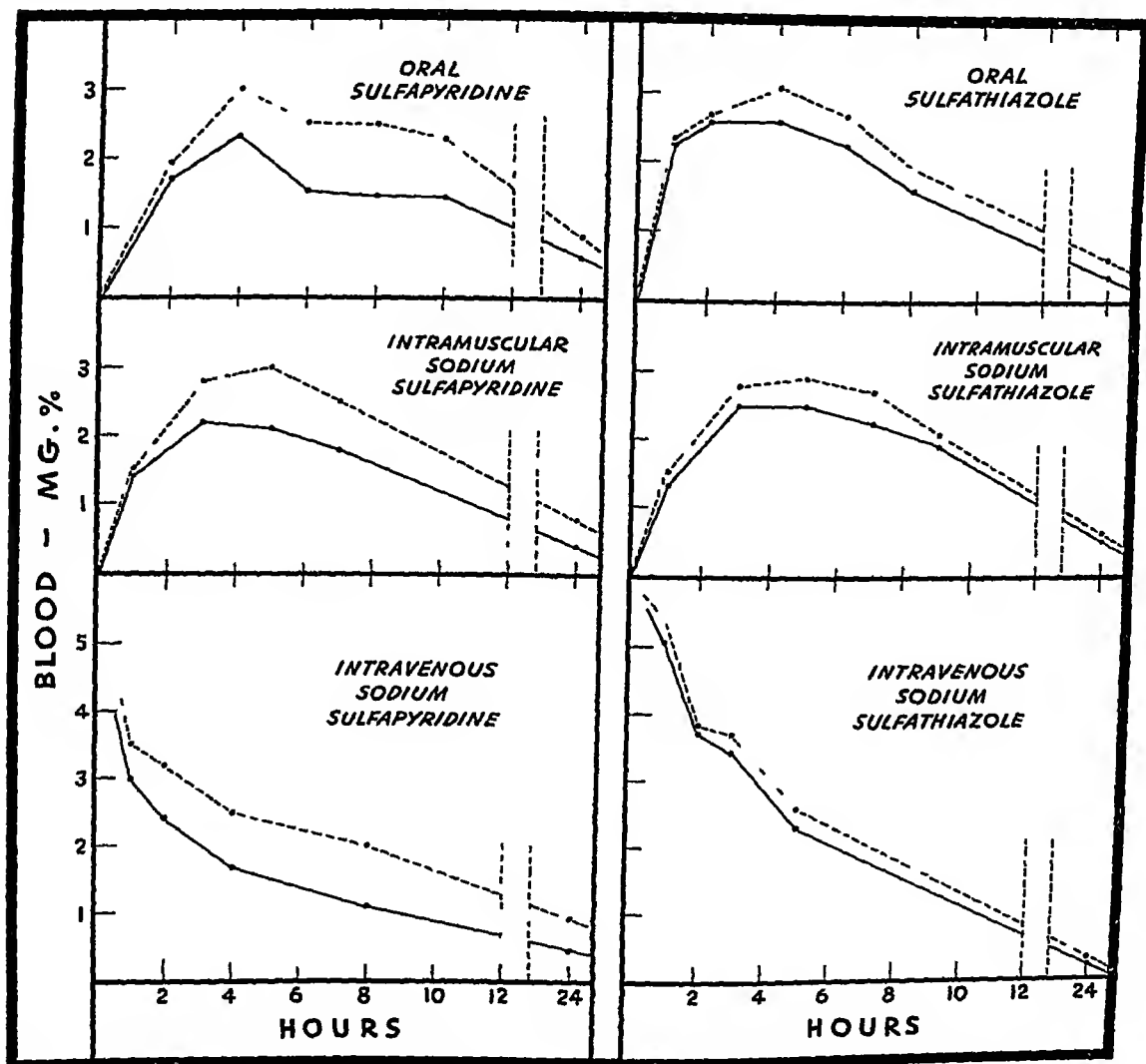


FIG 1 Curves of free and total blood concentrations following the administration of two grams of sulfapyridine or sulfathiazole by various routes

There were no toxic reactions except for occasional mild nausea and one instance of vomiting an hour after administration of an intravenous dose of sodium sulfapyridine.

CLINICAL OBSERVATION

We have previously reported the clinical use of intramuscular sodium sulfapyridine in a series of 25 cases.⁴ Since that time we have enlarged this series to over 200 cases, representing more than 1500 intramuscular injections and including also the use of intramuscular sodium sulfathiazole in the same manner. Recently we have used sodium sulfadiazine intramuscu-

larly in a small series of cases with equally good results. Many of the patients received their medication by the intramuscular route exclusively, in others the intramuscular method was substituted for oral administration for a varying number of doses. This group of patients represented various types of infections for which sulfonamide medication would ordinarily be indicated, pneumococcal infections constituted the largest portion of the group.

The drug was prepared freshly each day as a 33 1/3 per cent solution in distilled water and injected deeply into the gluteal muscles or into the muscles of the thigh beneath the fascia lata. Originally our maintenance dosage schedule was 3 c.c. of the solution every four hours, but more recently we have maintained effective blood levels on a régime of 6 c.c. at six or eight hour intervals. In some cases isolated intramuscular injections were substituted gram for gram for oral medication.

Clinical results paralleled those obtained with oral medication. Toxic effects were no more frequent after intramuscular than after oral administration. In the group in which the intramuscular route alone was used, the incidence of dermatitis, hematuria, and leukopenia was somewhat lower than has been our experience with the oral route.⁵ The most striking effect was the marked decrease in the incidence of nausea and vomiting (7.4 per cent). In several instances of severe nausea and vomiting after oral administration, relief was obtained when the change was made to intramuscular medication.

In the entire series two necrotic sloughs followed intramuscular injection. In both the drug was given, unsupervised, by a nurse with a short needle into the subcutaneous fat. In no case of correct administration into the muscular tissue was there any necrosis or inflammation. The degree of discomfort with the procedure was no greater than is seen with many drugs commonly given by the intramuscular method. Neither in rabbits nor in human subjects have we been able to demonstrate signs of inflammation or degeneration on microscopic examination of muscular tissue taken after intramuscular injection of sodium sulfapyridine.⁵

DISCUSSION

In general, our oral and intravenous studies agree with results of other investigators,^{6, 7, 8} both in general outline of the curves and great variability among individuals. Our purpose, however, has been to include the action of the drugs after the intramuscular method of administration and to compare the efficiency of this route with others.

Approximately the same blood concentrations are obtained by the intramuscular and oral routes, a fact shown in our clinical use of the method. Effective blood levels are maintained longer by intramuscular injection than by oral administration, thereby permitting a wider spacing of doses. Clinically we obtained effective results on a six and even eight hour dosage schedule.

The variation among individual subjects prevented drawing conclusions about comparative urinary excretion by the different routes

The striking decrease in the incidence of nausea and vomiting with intramuscular use reopens the question of local or central origin of this distressing complication. If nausea and vomiting after sulfonamide therapy were of central origin, one would expect the incidence to be the same for all methods of administration, provided equal blood levels were reached. However, the lowered incidence after parenteral use with equally high blood concentrations points very strongly to the conclusion that the principal etiological factor is local irritation of the gastric mucosa. Strickler and associates⁹ have shown the drug to be present in the stomach in fairly high concentrations following intravenous administration of sodium sulfapyridine. This could account for the few instances of nausea and vomiting which are encountered with parenteral use of the drugs.

Frequently in the course of clinical practice it is found that oral administration of the sulfonamides is not practicable. In comatose or delirious patients, after certain types of abdominal surgery, and in many patients, especially children, with severe nausea and vomiting, oral medication is undesirable and often impossible. Under such conditions a practical and effective means of parenteral administration of the drugs is necessary.

There are several objections to intravenous use of the drugs. In spite of the high initial concentration the blood level falls rapidly and a therapeutic level is not maintained as long as after an equal oral or intramuscular dose. Should any of the solution be introduced into the surrounding areolar tissue, necrosis, abscess formation, and ulceration may occur. When sodium sulfapyridine was first introduced, Marshall and Long¹⁰ pointed out the dangers of sloughing after intravenous administration. The technical difficulties of this route are obvious with small veins, as in infants, children, obese women, and elderly patients. These difficulties add to the danger of the perivascular supporting tissues being infiltrated with the drug. Moreover, the highly alkaline sodium salts of these drugs tend to sclerose the veins, and repeated injections often render them unfit for further use.

Certain precautions must be taken, however, in the intramuscular use of the sulfonamides. Because of their high alkalinity, the drugs may produce necrotic sloughs, if they are deposited into the subcutaneous tissue. Care must be taken to use a long needle and to deposit the entire dose into the muscle. Unsupervised injection cannot be given by one unfamiliar with the necessity for correct technic. British observers¹¹ report paralysis and foot-drop from damage to the sciatic nerve by direct irritation of the drug injected intramuscularly. A little care in choosing the site of injection to avoid the region of the sciatic nerve will prevent this complication. The intramuscular injection of any irritating substance should be made deeply into the body of the gluteus medius muscle at a point midway between the greater trochanter and the iliac crest. Thigh injection should be made on the lateral aspect of the mid-thigh region through the fascia lata into the vastus lateralis muscle.

We wish to emphasize that the intramuscular method of administering sulfonamides is seldom the route of choice. Oral administration of any drug is always to be preferred. However, when there are gastrointestinal complications, or when it is difficult, impossible, or impractical to give drugs intravenously, an alternative route is desirable. It has been our purpose to show that sulfonamides may be given into the muscles, thus providing an additional safe and effective route of administration.

SUMMARY AND CONCLUSIONS

1 Studies are presented comparing the absorption and excretion of sulfapyridine and sulfathiazole by intramuscular, oral, and intravenous administration.

2 Absorption of the drugs after intramuscular injection is adequate and compares favorably with other routes.

3 No conclusion can be drawn as to the comparative urinary excretion by the different methods of administration.

4 Clinical experience with the intramuscular route is reviewed.

5 Certain necessary precautions with the intramuscular use of these drugs are emphasized.

6 The intramuscular administration of the soluble sulfonamide drugs presents certain advantages over other methods and offers a safe and effective alternate route when used correctly.

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PAINFUL FEET *

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THIS article is written for the practicing physician who has had but little experience in orthopedic surgery but has patients who complain about their feet. If referring them to an orthopedic surgeon is out of the question it is up to him to offer relief if that is possible, and it is because so many of these cases can be relieved by the family doctor that suggestions are here offered as to how to proceed. A somewhat "sketchy" review of the anatomy, mechanics and functions of the foot will be followed by directions as to the examination, diagnosis and treatment.

For the purpose of this article it is necessary to keep in mind only the three principal axes of movement of the foot. They are the transverse, through the ankle joint, the longitudinal, through the subastragaloid joint, and the vertical, through the mediotarsal joint. The astragalus articulates with the tibia and fibula above, the os calcis below and the scaphoid in front. The articular surface which fits into the mortise formed by the tibia and fibula is narrow in its posterior part so that, although there is no lateral movement with the foot at a right angle to the leg or in dorsal flexion, there is slight lateral movement with the foot plantar flexed. That is why a high-heeled shoe makes the ankle less stable and more easily subject to strain than does the low-heeled shoe. Except for very slight rotation in full plantar flexion, which need not be considered in this article, movement at the ankle is in an anteroposterior plane, that is, around a transverse axis passing from the tip of the external malleolus to a point one-half inch below the tip of the internal malleolus. The joint between the astragalus and the calcaneum is divided by the dense interosseous ligament. Movement at this joint is around an axis passing obliquely from in front and medially, backward and laterally. (In the left foot, about 1 30 to 7 30 on the watch dial.) The movements, therefore, are inversion and eversion and take place in the subastragaloid and astragaloscaphoid joints. The astragaloscaphoid articulation should be considered with the calcaneocuboid articulation as motion in these two joints is usually concomitant. These four bones make up the mediotarsal joint. Motion takes place about a vertical axis, abducting and adducting the forefoot on the hindfoot. The articulations of the cuneiforms and the metatarsals need not be here taken up.

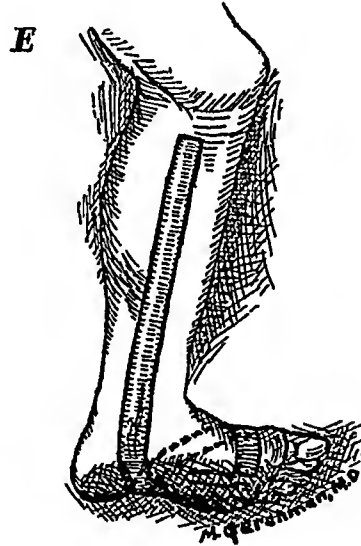
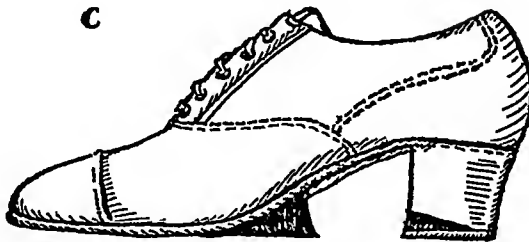
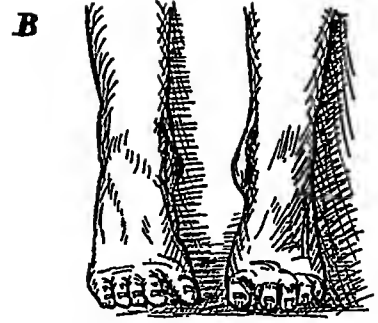
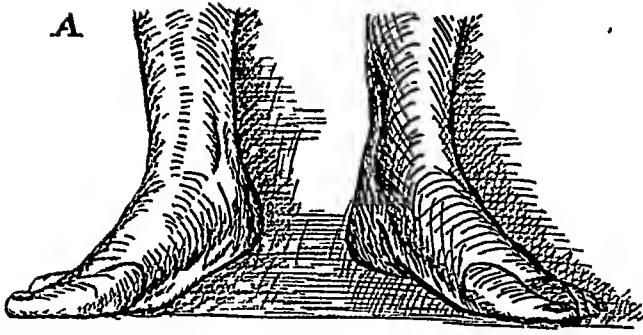
The functions of the foot are support and propulsion. With the muscles relaxed the ligaments prevent displacement. They become tight when the normal limit of movement in any joint is reached. The muscles arrange the bones, i e., place them in the proper relationship to one another for any purpose. In an active foot, in walking for example, the purpose or function of

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the foot changes a number of times, and the muscles must, therefore, change the bony relationship a number of times. In each step taken the foot receives the shock of contact with the ground, supports the body, raises the body and thrusts it forward, and is itself again brought forward, completing the cycle. Therefore, some groups of muscles direct the forefoot and hold the bones in the best possible relationship to receive the thrust of the body, others raise the hindfoot and others propel the body forward. Most of the muscles take part in each function to some extent. A fact to be noted here is that all physiological structures need both exercise and rest to be healthful—that is normal. Neither prolonged use nor prolonged rest is good for bone, ligament or muscle. With the foot at rest, as when one sits on a table with the foot hanging relaxed, it will be noted that the toe is slightly lower than the heel and the forefoot slightly adducted. In running, where this relaxed position is assumed after the foot leaves the ground and comes forward for the next step, the muscles do not become tired as quickly as in heel and toe walking. A dog-trot, for any distance, is less tiresome than walking. One is easily persuaded that heel-and-toe walking does jar the central nervous system. A man with a throbbing headache walks on his toes to avoid this jar and, in the absence of the headache, the jar must be there just the same. Hence, the adoption of rubber heels. The tap-tap-tap of high heels must be like slight but continuous hammer blows. This heel-toe walking is always used with pronated feet and it is hard to overcome, old habits are hard to change and most footwear prevents any change. With the foot in a stiff shoe the normal movements in the directions of eversion and inversion, abduction and adduction are impossible, to perform its normal functions the foot demands freedom of movement.

In standing, the ideal position for support of the body is with the feet parallel and about four inches apart. It is better to toe in markedly than to toe out ever so slightly. With the foot in abduction, the anteroposterior plane containing the center of gravity is brought to the medial side and thus away from the strongest part of the forefoot, tending at the same time to roll the foot downward on the medial side (eversion) and to push the forefoot into further abduction. This also puts a strain on the calcaneoscaphoid ligament and causes intra-articular pressure at the calcaneocuboid joint. As a result, pain may be felt about the strained ligament and compressed joint and callosities will form on the lateral side over the head of the fifth metatarsal and under the big toe joint from continuous pressure.

In walking correctly, the heel is raised and rotated inward and upward on the subastragaloid axis—the longitudinal axis—and thrust outward, by abduction at the mediotarsal joint, through the vertical axis. As the forefoot is held firmly to the ground the abduction is expressed in this movement of the hindfoot. Then, as the transverse plane of the body advances over the foot, the ground is spurned by the forefoot. When the foot is to be brought forward for the next step all of its muscles should be relaxed and,



A Tip-toe position with toes pointing outward. All movements are confined to the ankle and the metatarsophalangeal joints. The foot is raised "en bloc."

B Tip-toe position with feet pointing straight ahead. Every joint in the foot is functioning. The foot is plantar flexed, adducted and inverted. The forefoot being held fast to the ground, the movements are expressed mostly by the position of the hindfoot.

C Wedges applied. Heel wedge raises up anteromedial corner of heel one-eighth, one-sixth or one-quarter inch. (Rarely one-half inch is needed.) Sole wedge does not raise medial side of sole. Its purpose is to fill in the space between the shank of the shoe and the floor, after the heel wedge is applied.

D An inflexible shank made flexible by the removal of a wedge-shaped piece. The shank should be narrow as well as flexible. The extension of the wedges is also shown.

E Strapping the weak foot with adhesive plaster. The foot is relaxed, the knee being

as explained above,¹ the toe will be slightly in advance of the heel as it reaches the ground. In all athletic games the foot is used in this way, but modern shoes compel us to walk without using the functions of the foot except for dorsal and plantar flexion of the ankle joint and extension and flexion of the metatarsophalangeal joints.

An arthritis of one or more joints of the foot, as in any other part of the body, will cause a varying degree of immobilization through muscular spasm. Before instituting treatment a differential diagnosis must be made between a traumatic and an inflammatory arthritis. This is particularly true when the forefoot is immobilized in the position of abduction. Overcoming the deformity by stretching the spasmodic peronei, which is the correct treatment of a spasmodic flat-foot, would be erroneous for an infected astragaloscaphoid joint.

In the diagnosis and treatment of painful conditions of the feet a history of the case is of great value. If the feet were painless until recently, perhaps within a few weeks or even a few months, did a change in the amount the feet were used seem to cause the pain? If so, probably the feet were weak before but, because they were used but little, not much attention was given to the discomfort. A change in the style of foot apparel may be a cause, especially in the height of the heel. Are the feet painful upon first arising in the morning or are they comfortable until after walking a few blocks, and does the pain radiate up the backs of the legs? During the night the muscles are relaxed—they are not active in guarding the astragaloscaphoid joint from strain—and the pain is felt immediately when this joint becomes weight-bearing. After hobbling about a bit, the pain will lessen as the spasm returns and the joint is restricted in motion. Such a foot will be again painful after much use, perhaps in the afternoon of an active day. On the other hand, there may be no pain at all upon arising in the morning and none will appear until work for the day has been started. The patient will report having walked perhaps an eighth of a mile when his calves began to hurt so severely that he had to stop and even sit down. A frequent cause of this pain is lack of normal dorsal flexion of the foot, though there may be little or no deformity in any of the joints. Yet it must be borne in mind that these pains are sometimes the precursory symptoms of circulatory disturbances. Limitation of dorsal flexion, as will be shown later on, is the basic factor in many cases of weak and painful feet, and this condition should be suspected if the history shows that the patient feels that he must wear heels even on slippers, that high heels on shoes are more comfortable than

flexed to shorten the gastrocnemius, then held in dorsal flexion at a right angle, adducted and inverted. Three straps are used, each one and one-half inches wide and long enough to reach almost to the knee. The first strap is placed around the forefoot, its distal edge slanting to follow the base of the toes. It grasps the forefoot firmly and crosses the plantar surface from the lateral to the medial side and up the medial side of the leg. The second strap reinforces the first and overlaps it three-quarters inch. The third strap begins above the lateral malleolus, comes down, under the heel, and up the medial side of the leg. The purpose of the strapping is to check abnormal movements, thus teaching normal joint and muscular sense and supporting atrophied muscles.

low, that pain was referred up the leg and that backache was frequently present. Inquiry should be made as to how much the feet have been used, in athletics, long walks, or much standing.

Examination When standing, with the shoes on, does the patient toe out, are the legs straight and the patellae facing forward (that is are the legs rolled outward from the hips) and, in rising on tip-toe, does he adduct the foot or is movement restricted to the metatarsophalangeal and ankle joints? Examining the shoes, note if the soles are worn more toward the medial side than laterally and where the heels are worn down at the back. If the wear has been on the lateral side it shows that the patient walks with the toes out. Are there longitudinal creases in the leather just back of the position of the great toe? Such creases are made by abduction of the forefoot with consequent lowering of the arch. Standing, in bare feet, are the sides of the heels vertical or are the outer sides sloping downward and outward? Are the feet abducted? Do the toes lie flat against the ground? Rising on tip-toe are the metatarsal joints adducted and are the plantar surfaces of the heel inverted? Sitting on a stool at a right angle to the patient, so that the patient's ankle may rest on the knee of the examiner, note any puffiness or swelling, the color of the skin, especially of the toes, the patency of the dorsalis pedis and the posterior tibial arteries, the location of all callosities. Callosities are due to pressure. If found under the heads of the five metatarsals, they are always due to a shortened heel cord, on the outer side of the foot, opposite the head of the fifth metatarsal, they are due to pressure of the foot against the shoe from abduction, beneath and to the medial side of the big toe they are due to pressure caused by eversion. The passive movements in the three principal axes are now tested. With the foot in slight inversion and adduction and the knee in full extension, dorsal flexion should be to 90 degrees or less. Abduction, adduction, eversion and inversion should be free, normal in range and painless. Is the calcaneocuboid or the astragaloscaphoid joint painful to pressure? Manipulate the toes to determine their freedom of motion. Freedom of movement of the first metatarsophalangeal joint is essential to comfort and its absence may be the chief factor in causing abduction.

Now if it is quite evident that, in standing and walking, the foot is used in the position of eversion and abduction, diagnosis of "weak foot" or "pronated foot," both being practically the same, may be made and treatment instituted. However, if there is evidence of circulatory trouble or heat or swelling or muscular spasm limiting any of the movements, then an exact diagnosis of the underlying cause of such a condition must be made before any other procedure. If the forefoot is held in abduction by spasm of the peroneals, hot foot-baths and absolute rest for a few days should restore free passive movement, and if they do not, roentgenograms should be taken and a careful differential diagnosis made between spasmodic flat-foot and bone or joint disease.

Treatment With all movements free and normal in range, with the foot in the standing position in eversion, as shown especially by the heel, and in abduction, as shown by the forefoot being turned outward, treatment is directed toward restoring the foot to its normal position and keeping it there, at the same time forcing it to function normally. This is accomplished by altering the shoes, strapping the feet and obtaining the cooperation of the patient. The weakened muscles, especially the tibials, must be built up, the joint sense must be reeducated and normal function restored. A wedge is placed on the anteromedial part of the heel, its purpose being to restore the normal inclination of the calcaneum. It should be one-eighth to one-quarter inch at its thickest part, depending upon the degree of rotation of the calcaneostragaloid joint. Usually, it is better to use a one-quarter inch wedge at first and reduce it as improvement progresses. A sole wedge is applied, filling in the space between the first metatarsal and the supporting surface. This may be flared medially, and the more it extends medially the more will it help to prevent eversion and abduction. A good cobbler can give a flare of at least one-sixth inch. This wedge does not tilt up the inner border of the foot as does a wedge along the medial part of the sole of a shoe. It allows the sole to lie flat on the ground in the same plane as the bottom of the heel *after the heel wedge is applied*. The sole wedge must be of such a length as to prevent the metatarsal from being lowered at its proximal end. From two to two and one-half inches is usually satisfactory. The shanks must be flexible, so flexible as to offer no resistance to the adducting and inverting of the foot. In these cases the muscles used in the movements of adduction and inversion are usually so weak that at first any resistance may be enough to prevent their action. Most shoes have a strip of steel in the shanks. This is removed and, if its removal does not make the shoe fully flexible, a V-shaped piece is cut out of the shank. The shank cannot be too flexible.

The reason shoe manufacturers do not usually make the shanks flexible is that most people still toe out, using only the ankle joint and the metatarsophalangeal joints, and consequently the weight at the midtarsal would soon distort and make ugly a shoe that was built with no stiffening in the shank. It is apparent, therefore, that this line of treatment is not appropriate for the patient who will not carry it out. Normal functioning of the foot demands freedom of use of all joints and, conversely, a foot used abnormally needs artificial support. Adhesive strapping is used to help to direct the weakened muscles and to reeducate the joint senses. For the first few weeks it will be necessary to keep the strapping constantly applied and thereafter it will need to be applied intermittently, to prevent the resumption of old habits. With the shoes wedged and the strapping applied, the patient is instructed always to use the foot with the toes pointing inward. The foot functions properly with the toes pointing straight ahead, but it is better to instruct the patient to try to toe in.

Specific exercises are unnecessary if the patient indulges in any sports which keep him on his toes. Dancing is splendid for weak feet. Standing is hard on the structures of the feet as they are subjected to continuous work and strain. It can be explained to the patient that every physiological structure needs both work and rest—the heart being a good example—and that, in standing, exhaustion can be prevented by constantly changing the supporting muscles and ligaments, by raising the heels slightly, then resting on both heels and soles, then standing on the outer borders of the feet. This, if repeated every few minutes, will be of great benefit.

There is one factor which is present in many cases of painful feet, which may be a cause of metatarsalgia and certainly is an obstacle to overcoming abduction, and that is a shortened heel cord. If dorsal flexion is arrested at 90 degrees, the arrested movement thrusts the weight of the body against the forefoot, like a blow at each step. If dorsal flexion is limited to 93 degrees or more, it is impossible to walk without abducting the foot, unless the heels are of such a height as to make dorsal flexion necessary to only 95 degrees.

If the above treatment is persisted in, the gastrocnemius will, in many cases, be stretched by use in the corrected position, if not, other methods must be used to lengthen the calf muscles.

It should be kept in mind by all physicians that pronated feet may be a contributing factor in faulty posture, backache and muscular pains of the lower extremities.

THE COMPARATIVE VALUE OF CALCIUM GLUCONATE, MAGNESIUM SULFATE, AND ALPHA LOBELINE HYDROCHLORIDE AS AGENTS FOR MEASUREMENT OF THE ARM TO TONGUE CIRCULATION TIME IN 50 PATIENTS WITH AND 50 PATIENTS WITHOUT HEART FAILURE *

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THE arm to tongue circulation time is now recognized as a valuable means of determining the efficiency of cardiac function. It is also useful in the study of other diseases in which the velocity of blood flow is altered. Specifically, it measures the time required for the passage of a drug from the point of injection in one of the veins of the antecubital fossa through the systemic veins, the right side of the heart, the pulmonary system, the left side of the heart, and the systemic arteries to a point of perception, usually the tongue.

In conditions in which the velocity of blood flow is diminished, the arm to tongue circulation time is prolonged. This occurs most commonly in congestive heart failure, so that in general the test has its greatest use in this condition. Its clinical value here lies in the aid afforded in confirming the diagnosis of heart failure in questionable cases and in following the progress of any case. On the other hand, the test is perhaps equally valuable in a negative way for excluding the diagnosis of heart failure in patients with dyspnea or other symptoms which suggest cardiac decompensation¹. It should be noted that in certain cases of heart failure the circulation time may not be prolonged. Hyperthyroid heart disease² and beriberi heart disease³ are the best known etiologic varieties which illustrate this.

Other causes for prolongation of the arm to tongue circulation time include conditions in which the venous return to the heart is obstructed, such as cardiac compression and local lesions of the superior vena cava or its tributaries. Polycythemia rubra vera⁴ and myxedema⁵ also cause generalized slowing of the velocity of blood flow.

The arm to tongue circulation time is decreased in conditions in which the blood flows more rapidly. This is true in hyperthyroidism,² severe anemia,⁴ and fever. In hyperthyroidism, the test has obtained some popularity as a simple means of confirming the diagnosis.

The drugs used for measurement of the arm to tongue circulation time include calcium salts and magnesium sulfate which produce a sensation of warmth in the patient's throat and tongue, saccharine which causes a sweet taste, decholin which gives a bitter taste, sodium cyanide which causes a

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gasp when the drug reaches the carotid sinus, and lobeline which also acts on the carotid sinus to produce a paroxysm of coughing. Various reports^{6, 7, 8, 2, 9, 10} indicate that all of these drugs give approximately the same results for measurement of the circulation time in normal persons. The range most usually quoted for the normal arm to tongue circulation time is from 9 to 16 seconds. Obviously in a strict sense, all of these agents cannot be said to measure the arm to tongue circulation time because not all of them have the tongue as their point of perception. However, for practical purposes it has been assumed that the terms, arm to tongue, arm to throat, and arm to carotid sinus, may be used interchangeably. In our opinion any one of these terms is preferable to the term, total circulation time, which lacks the anatomical definitiveness of the former. In this paper, the term, arm to tongue circulation time, has been adopted.

A drug that is to be used in clinical practice for measurement of the arm to tongue circulation time should fulfill certain requirements.¹¹ It should be non-toxic in the dose employed and should be known to have no undesirable effect on the pathological condition being studied. It should have a minimum of unpleasant side effects and should be eliminated rapidly enough so that it can be used repeatedly. It should have an end point which is easily recognized, and the number of cases in which the drug fails should be minimal. The drug should be readily available for general use and preferably should be inexpensive. All of the drugs mentioned above in connection with measurement of the circulation time fulfill these requirements adequately enough to justify their employment. However, saccharine and sodium cyanide are not readily available for general use except in large clinics or hospitals where they can be prepared inexpensively to order.

We have previously reported¹² observations which demonstrate that measurements of the arm to lung circulation time by means of ether may be significantly different from those obtained with paraldehyde in patients with heart failure. Kvale and Allen¹¹ have compared sodium cyanide and a calcium-magnesium-sodium solution for measurement of the arm to tongue circulation time. They found that in normal persons an inherent error of about three seconds exists in measurements obtained with sodium cyanide. It has been our interest, therefore, to compare the results obtained in measurement of the arm to tongue circulation time by means of three readily available agents, namely, calcium gluconate, magnesium sulfate, and lobeline. The object of this study has been to determine whether or not these three drugs would give equal results when used in the same patient. The demonstration has been attempted in 50 patients without apparent cause for alteration of the velocity of blood flow and in 50 patients with heart failure.

Technic Measurement of the arm to tongue circulation time was obtained in each case after the patient had been resting in bed for at least one-half hour. The patient was in supine position at the time of the test, with the arm in which the injection was to be made abducted through an angle of 45 degrees and in such position that the veins of the antecubital fossa were at

or below the level of the right auricle. One of the veins was entered with a 20-gauge needle, 30 seconds were allowed to elapse after removal of the tourniquet in order to permit restoration of blood flow, and then 5 c c of 20 per cent calcium gluconate* were injected *as rapidly as possible*. The time from the beginning of the injection until the patient called "Now" at the moment of feeling a sense of warmth in the throat and tongue was measured by means of a stopwatch. A period of several minutes was then allowed to pass, in order for the sensation produced by the calcium gluconate to disappear. During this short period, the needle remained in the vein and a small amount of physiologic saline was injected slowly in order to prevent clotting within the lumen of the needle. Following disappearance of the feeling of warmth produced by calcium, 5 c c of 10 per cent magnesium sulfate were injected *as rapidly as possible* and the same procedure followed as for calcium. Again, after passage of a sufficient interval for disappearance of the sensation of warmth produced by the magnesium solution, 5 mg of alpha lobeline hydrochloride* were injected through the same needle in the same manner. The time that elapsed from the beginning of the injection until the patient began a short paroxysm of coughing was measured with a stopwatch. In those instances in which 5 mg of alpha lobeline failed to provoke coughing after an interval of about two minutes, 7.5 mg of the drug were injected for a repetition of the attempt to measure the circulation time. In all cases, a careful watch was kept for other possible manifestations of reaction to the alpha lobeline, such as grimacing, hyperpnea, and gasping. The end point which was observed first was used for the circulation time measurement. In those cases in which the circulation time measurement by means of alpha lobeline seemed unusually shorter than the measurements obtained with the other drugs, it was suspected that the arm to lung circulation time had been measured. An attempt to confirm this suspicion was made in such cases by measuring the arm to lung circulation time with ether.

CLINICAL RESULTS

The results of measurement of the circulation time with calcium gluconate, magnesium sulfate, and alpha lobeline in 50 patients who had no cause for a reduction of the velocity of blood flow are shown in table 1. The results of similar measurements in 50 patients with heart failure are shown in table 2.

In the 50 patients who did not have heart failure, there was no instance in which all three of the drugs failed to produce an end-point. There were 11 cases in which 5 mg of alpha lobeline failed to give an end point. In all but three of these, 7.5 mg of the drug were effective. However, there were two additional cases in which alpha lobeline yielded a record of the arm to lung circulation time, as shown by comparison with measurements made by

* Calcium gluconate as ampules of 20 per cent Neocalglucon and alpha lobeline hydrochloride in ampules of 1 per cent solution were supplied by the Sandoz Company.

TABLE I
Cases without Heart Failure

Case No	Diagnosis	Arm to Tongue Circulation Time (Seconds)			
		Neocal-glucon	Magnesium Sulfate	Alpha Lobeline	
				5 mg	7.5 mg
1	Metrorrhagia	13.8	14.8	No end point	15.0
2	Prostatism	15.0	17.0	No end point	13.0
3	Hypertension	10.2	10.0	No end point	No end point
4	Hypertension	13.0	14.2	11.2	
5	Hypertension	12.0	15.0	10.6	
6	Nephritis	11.0	11.6	No end point	No end point
7	Carotid sinus syndrome	12.8	11.8	9.4	
8	Normal control	10.0	10.0	8.2	
9	Hypertension	No end point	14.0	(G)15.0	(G)15.0
10	Hypertension	14.6	14.6	No end point	No end point
11	Alcoholism	12.0	11.0	10.6	
12	Pulmonary tuberculosis	14.0	18.0	17.4	
13	Hypertension	10.8	11.0	10.8	
14	Prostatism	14.8	14.2	(G)15.0	
15	Hypertension	15.0	15.0	(G)14.0	
16	Hypertension	No end point	20.8	No end point	14.8
17	Rheumatic heart disease	15.6	16.0	15.0	
18	Parkinsonism	15.2	15.6	(G)13.0	
19	Rheumatic heart disease	15.0	13.6	12.2	
20	Cirrhosis	14.0	13.0	12.8	
21	Cerebral thrombosis	13.8	15.0	*6.0	
22	Hypertension	17.2	18.2	(G)10.0	
23	Carcinoma of pancreas	14.6	14.8	14.2	
24	Hypertension	15.0	15.4	12.0	
25	Hypertension	17.0	17.0	15.0	
26	Gastric carcinoma	15.0	15.8	11.0	
27	Hypertension	18.6	18.0	No end point	14.8
28	Hysteria	14.0	16.0	12.4	
29	Ménière's syndrome	10.2	12.2	*6.8	
30	Obesity	15.0	16.5	No end point	(G)13.0
31	Chronic glomerulonephritis	13.2	13.2	No end point	(G)13.0
32	Hypertension	18.0	18.0	14.0	
33	Hypertension	15.6	16.6	15.0	
34	Hypertension	16.0	16.8	11.2	
35	Bronchopneumonia	15.0	15.0	14.0	
36	Hypertension	17.0	16.2	16.0	
37	Hypertension	14.0	17.0	No end point	15.0
38	Diabetes mellitus	15.6	16.2	16.0	
39	Aortic aneurysm	16.0	14.0	No end point	(H)17.0
40	Pneumonia	11.6	11.4	9.2	
41	Pneumonia	12.0	12.4	10.0	
42	Alcoholism	14.0	14.2	12.0	
43	Hypertension	13.0	14.4	11.2	
44	Alcoholism	11.0	11.2	10.0	
45	Alcoholism	10.0	10.0	9.0	
46	Cerebral arteriosclerosis	11.0	11.6	10.0	
47	Manic-psychosis	10.0	10.2	10.0	
48	Alcoholism	12.8	13.0	11.0	
49	General paresis	12.0	12.4	11.4	
50	Alcoholism	14.0	14.0	12.2	

TABLE II
Cases With Heart Failure

Case No	Etiologic Type of Heart Disease	Arm to Tongue Circulation Time (Seconds)			
		Neocal-glucon	Magnesium Sulfate	Alpha Lobeline	
				5 mg	7.5 mg
1	Rheumatic	37.5	41.0	32.5	
2	Hypertensive	19.2	19.0	23.0	
3	Hypertensive	19.2	20.4	18.0	
4	Hypertensive	No end point	71.0	No end point	No end point
5	Hypertensive	60.8	58.0	No end point	No end point
6	Hyperthyroid	26.0	23.0	18.0	
7	Hypertensive	No end point	19.0	No end point	18.0
8	Hypertensive myxedema	41.0	42.0	No end point	40.5
9	Hypertensive	18.0	18.0	18.0	
10	Hypertensive	45.0	41.0	No end point	*26.0
11	Hypertensive	23.8	24.8	23.2	
12	Coronary artery sclerosis	25.2	No end point	33.4	
13	Hypertensive arterio-sclerotic	28.0	24.0	No end point	21.0
14	Hypertensive	35.0	47.0	No end point	40.8
15	Hypertensive	49.2	61.8	No end point	(H)75.0
16	Hypertensive	27.2	25.0	*15.8	
17	Syphilitic	20.6	25.6	20.6	
18	Syphilitic	70.0	69.6	No end point	75.4
19	Rheumatic	19.0	17.0	No end point	15.6
20	Syphilitic	24.0	25.0	19.2	
21	Hypertensive	No end point	No end point	No end point	49.0
22	Coronary artery sclerosis	21.6	20.0	No end point	(G)23.0
23	Hypertensive	30.0	24.0	20.0	
24	Hypertensive	33.2	34.8	No end point	*24.2
25	Rheumatic	No end point	No end point	No end point	No end point
26	Syphilitic	55.0	No end point	No end point	(H)50.0
27	Hypertensive arterio-sclerotic	No end point	No end point	No end point	No end point
28	Hypertensive arterio-sclerotic	23.0	23.0	No end point	(H)24.0
29	Hypertensive	47.6	45.6	No end point	47.0
30	Hypertensive	57.0	49.4	No end point	46.0
31	Rheumatic	24.2	19.0	18.2	
32	Rheumatic	No end point	No end point	No end point	28.0
33	Hypertensive	24.0	23.0	18.2	
34	Hypertensive	No end point	No end point	33.0	
35	Syphilitic	26.2	35.0	25.4	
36	Hypertensive arterio-sclerotic	23.0	21.0	No end point	No end point
37	Syphilitic	17.0	18.0	*10.0	
38	Coronary artery sclerosis	26.0	27.6	19.6	
39	Rheumatic	No end point	No end point	28.0	
40	Hypertensive	27.0	35.0	No end point	25.8
41	Hypertensive	26.8	24.0	No end point	22.0
42	Hypertensive arterio-sclerotic	30.2	25.6	*17.0	
43	Hypertensive	55.0	50.6	No end point	No end point ¹
44	Hypertensive	20.0	16.8	No end point	(G)15.0
45	Coronary artery sclerosis	20.0	18.8	19.6	
46	Rheumatic	No end point	No end point	No end point	No end point
47	Hypertensive	30.0	32.0	28.0	
48	Coronary artery sclerosis	50.0	54.0	No end point	45.0
49	Rheumatic	20.0	21.0	18.0	
50	Hypertensive	19.4	20.6	19.0	

means of ether Therefore, there were five cases (10 per cent) in which alpha lobeline failed to provide a record of the arm to tongue circulation time. Calcium gluconate failed to provoke any sensation in two cases (4 per cent) Magnesium sulfate was effective in all cases

Measurements of the arm to tongue circulation time by means of alpha lobeline ranged from 8.2 seconds to 17.4 seconds (average, 12.6 seconds) in the 45 cases in which the drug gave an end point There were 41 cases in which measurements obtained by means of alpha lobeline were shorter than those obtained with magnesium sulfate In 13 of these cases the difference between the measurements was three seconds or more The differences ranged from 0.2 second to 8.2 seconds, with an average difference of 2.2 seconds There were 35 cases in which alpha lobeline gave a shorter measurement of the circulation time than calcium gluconate In seven of these cases the difference was three seconds or more The differences ranged from 0.2 second to 7.2 seconds (average, two seconds)

Measurements of the circulation time with calcium gluconate in the 48 cases in which the drug was used successfully ranged from 10 seconds to 18.6 seconds (average 13.8 seconds) There were five cases in which calcium gluconate gave a shorter measurement than alpha lobeline, but in only one case was the difference three seconds or more The differences were from 0.2 second to 3.4 seconds (average 1.2 seconds) There were 29 cases in which calcium gluconate gave a shorter measurement than magnesium sulfate, but in only three cases was the difference three or more seconds The differences ranged from 0.2 second to 4 seconds (average, 1.1 seconds)

Measurements of the arm to tongue circulation time with magnesium sulfate in the 50 cases ranged from 10 seconds to 20.8 seconds, with an average of 14.4 seconds There were 10 cases in which magnesium sulfate gave shorter measurements than calcium gluconate In none of these was the difference as great as 3 seconds The differences were from 0.2 to 2.0 seconds (average, 0.9 second) There were two cases in which magnesium sulfate gave shorter measurements than alpha lobeline The differences were 0.2 second and 0.8 second

There were no alarming or unpleasant side effects from any of the drugs used in the 50 patients without heart failure The cough which resulted from administration of alpha lobeline was short and mild The sensation of warmth produced by calcium gluconate and magnesium sulfate passed away very quickly and was not disturbing

In the 50 patients who had clinical evidence of heart failure, there were three cases (6 per cent) in which all three of the drugs failed to produce an end point In the remaining 47 cases, the arm to tongue circulation time was found to be prolonged beyond the limits ordinarily accepted as normal There were nine cases (18 per cent) in which calcium gluconate failed There were also nine cases (18 per cent) in which magnesium sulfate failed There were 27 cases in which 5 mg of alpha lobeline failed to give an end point, but in only seven of these were 7.5 mg of the drug ineffective How-

ever, in five additional cases alpha lobeline gave a measurement of the arm to lung circulation time, so that there was a total of 12 cases (24 per cent) in which the drug failed as an agent for determination of the arm to tongue circulation time

There were 26 cases of heart failure in which alpha lobeline gave shorter measurements of the arm to tongue circulation time than magnesium sulfate. In 17 of these cases the difference was three seconds or more. The differences ranged from 0.8 to 10.6 seconds (average, 4.6 seconds). There were 26 cases also in which alpha lobeline gave shorter measurements than calcium gluconate. In 16 of these cases the difference was three seconds or more, and the differences ranged from 0.4 to 11 seconds (average, 4.3 seconds). There were 26 cases in which magnesium sulfate yielded shorter measurements than calcium gluconate. Nine of these showed differences of three

TABLE III
Normal Circulation Time, Measured with Calcium Gluconate,
Magnesium Sulfate, and Alpha Lobeline

Observers	Method	Range (Seconds)	Average (Seconds)
Goldberg ⁶	Calcium gluconate	10-16	12.5
Baer and Slipakoff ¹⁴	Calcium gluconate	9-16	12.7
Hussey, Cyr, and Katz	Calcium gluconate	10-18.6	13.8
Bernstein and Simkins ⁷	Magnesium sulfate	7-17.8	12.9
Hussey, Cyr, and Katz	Magnesium sulfate	10-20.8	14.4
Berliner ¹⁰	Alpha lobeline	5-18.0	9.3
Hussey, Cyr, and Katz	Alpha lobeline	8.2-17.4	12.6

or more seconds. The differences varied from 0.2 to 7.6 seconds (average, three seconds). In seven cases magnesium sulfate gave shorter measurements than alpha lobeline, and in four of these cases the difference was three seconds or more. The differences ranged from 1 to 13.2 seconds (average, 4.2 seconds). There were 17 cases in which calcium gluconate gave shorter measurements than magnesium sulfate, and in seven of these the difference was three seconds or more. Differences varied from 1 to 12.6 seconds (average, 3.9 seconds). In seven cases calcium gluconate gave shorter measurements than alpha lobeline, and in five of these the difference was three seconds or more. The range for the differences was from 1 to 25.8 seconds (average, 7.5 seconds).

As in the cases without heart failure, there were no disagreeable or dangerous side effects from the use of any of these drugs in patients with heart failure. As a matter of fact, some of the patients firmly believed that the administration of the drugs made them more comfortable.

DISCUSSION

From the studies reported here, it seems safe to conclude that the three drugs employed have an approximately equal usefulness in measurement of the arm to tongue circulation time. In the 50 patients who had no ap-

parent cause for a reduction in the velocity of blood flow, the ranges for the arm to tongue circulation time correspond closely with reports of other authors (table 3). The range for alpha lobeline is somewhat lower and the average arm to tongue circulation time is somewhat shorter than similar figures for magnesium sulfate and calcium gluconate. Furthermore, the circulation time measurements in the majority of the patients with heart failure were shorter with alpha lobeline than with either of the other two drugs. On the other hand, calcium gluconate and magnesium sulfate gave almost equal results in the two groups of cases. Therefore, when alpha lobeline is employed in clinical practice, it is necessary to remember that the results of measurement of the circulation time cannot be interpreted strictly in the light of previous experience with other agents, such as calcium, magnesium, and probably other compounds.

When any drug is used for the purpose of measuring the arm to tongue circulation time, failure of the drug to produce an end point is most commonly due to the fact that an adequate concentration does not reach the anatomical area of reaction or perception at any one time. This kind of failure may be due to the presence of a shunt which diverts the drug from the area of reaction, or to a lessening of the velocity of blood flow to such degree that the drug is too thoroughly diluted with the blood by the time it reaches the point of reaction, or to errors in the technic of injection, such as slowness of injection and failure of intravenous injection, or to the use of an insufficient dose. With regard to the matter of dosage of any of the agents used in measurement of the circulation time, certain standard doses have been recommended, more or less empirically. In some instances, dosage is limited because of toxicity, but the toxic limits for all drugs that have been used have not been determined as scientifically as might be desired. Ideally, the standard dose for each drug will be that amount which can be used safely and which will give a minimum of failures. Some such standard dose is necessary if measurement of the circulation time is to have value as an aid to clinical diagnosis for those who have not had wide experience in the use of the test. As experience is gained, it becomes possible to obtain accurate measurements while varying the dose of the drug employed according to the type of case. For example, measurement of the circulation time in a normal person by means of 20 per cent calcium gluconate will be the same with 2 or 3 c.c. of the drug as with 5 c.c. However, in a patient who has any cause for slowing of the circulation time, discrepancies will result from such variation in the dose of the drug. As a general rule, the use of larger amounts of any of these drugs will result in slightly lower figures for the circulation time. Further, when a specific amount of a drug is employed in a given patient, this same amount should be used later if the test is to be repeated. Otherwise, there will be no reliable basis for comparison of results. Other causes for failure of a drug used for measurement of the circulation time include insensitivity of the patient to the drug and failure or inability of the patient to cooperate during the test. In our series of 100 cases, the

percentage of failure was highest with alpha lobeline (17 per cent), next highest with calcium gluconate (11 per cent), and lowest with magnesium sulfate (9 per cent) Thirty of the 37 failures occurred in the patients with heart failure In cases in which one drug fails to provide an end point for measurement of the circulation time, it is desirable to employ another drug Thus, in only three of the 100 patients in our series did all three of the drugs fail This kind of occurrence probably will be limited to cases in which there is extreme slowing of the circulation

Alpha lobeline has one important advantage over the other two drugs used in our study This is the fact that it gives an objective end point It has, therefore, a unique field of usefulness in uncooperative patients and in patients who are unconscious or stuporous Its value is enhanced by the knowledge that a grimace is sometimes the only indication of its end point In our experience, hyperpnea is not reliable as an end point This phenomenon can be observed in practically all of the cases in which the drug is used, but many seconds after the appearance of a grimace or cough Hence, in cases in which hyperpnea is the only reaction to administration of the drug, it is safe to assume that the drug reached the carotid sinus long before the reaction appears This assumption is supported in such cases by the marked discrepancy between measurement of the circulation time by means of alpha lobeline and that obtained with calcium gluconate or magnesium sulfate Apparently the only objections to the use of alpha lobeline for determination of the arm to tongue circulation time are that it often fails in a dose of 7.5 mg, and it occasionally provides a measurement of the arm to lung circulation time The first objection probably can be solved in part by the use of larger doses Probably 7.5 mg are always safe as an initial dose for adults of average size, and doses up to 12 mg have been used¹⁰ The second objection is apparently insurmountable and may cause considerable confusion in interpretation of results unless they are verified routinely by means of another drug We have seen no unpleasant effects from the administration of alpha lobeline Hemoptysis has been mentioned as the only definite contraindication to the drug¹⁰ However, two patients in our series who were having hemoptysis were not adversely affected by alpha lobeline, nor were any of the patients with acute or chronic inflammatory conditions in the lungs We have not found any necessity for a delay between injections when the use of the drug is repeated in the same patient

From a study of the statistics in tables 1 and 2, it seems safe to say that calcium gluconate and magnesium sulfate give results which are equally satisfactory for measurement of the arm to tongue circulation time Neither has an unpleasant effect, and apparently neither is dangerous in the doses recommended However, a theoretical objection has been raised to the use of calcium in patients receiving digitalis¹³ This objection is based on the knowledge that calcium and digitalis have an additive effect on the heart Nevertheless, the dose of calcium gluconate recommended for measurement of the circulation time seems to be entirely without danger

SUMMARY AND CONCLUSIONS

1 The results of measurement of the arm to tongue circulation time with alpha lobeline, calcium gluconate, and magnesium sulfate have been compared in 50 patients without cause for slowing of the circulation and in 50 patients with heart failure

2 Alpha lobeline gave somewhat shorter measurements than calcium gluconate and magnesium sulfate in both groups of cases, but failed to provide an end point more often than either of the other drugs. Furthermore, the fact that it sometimes measured the arm to lung circulation time seems to detract from its value for routine use. Its chief advantage consists in the objectivity of its end point

3 Calcium gluconate and magnesium sulfate gave approximately equal results. They seem to be equally valuable for routine use in measurement of the arm to tongue circulation time, and perhaps are more valuable in this respect than alpha lobeline

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CASE REPORTS

CALCINOSIS TREATED BY PARATHYROIDECTOMY*

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SUBCUTANEOUS calcinosis, a disease tending to serious bodily disability, presents a most difficult therapeutic problem. It is usually the sequel to dermatomyositis or some inflammatory disease in the skin or subcutaneous tissue, and produces difficulty by interfering with proper skeletal function by restricting the movements of muscles and tendons. The circulation of the skin and surrounding tissues may be disturbed and, at times, ulceration and infection may take place in the region of the calcium deposits.

Since the calcium deposits are usually considered to be fixed and the destruction of muscles and tendons irreparable, any type of treatment seems almost doomed to failure. Acid salts, such as ammonium chloride, have been used in an attempt to draw calcium from its deposits into the blood stream where it can be excreted normally. This method seems rational, but the results are usually disappointing. The production of ketosis, another method of attacking calcium stores, was reported to be successful in a case by Kennedy.

Ramsdell reported striking results in a young girl with calcinosis, following the production of tetany induced by unilateral parathyroidectomy. This plan of treatment likewise has as its motive the mobilization of calcium. It was utilized in the case herein reported.

CASE REPORT

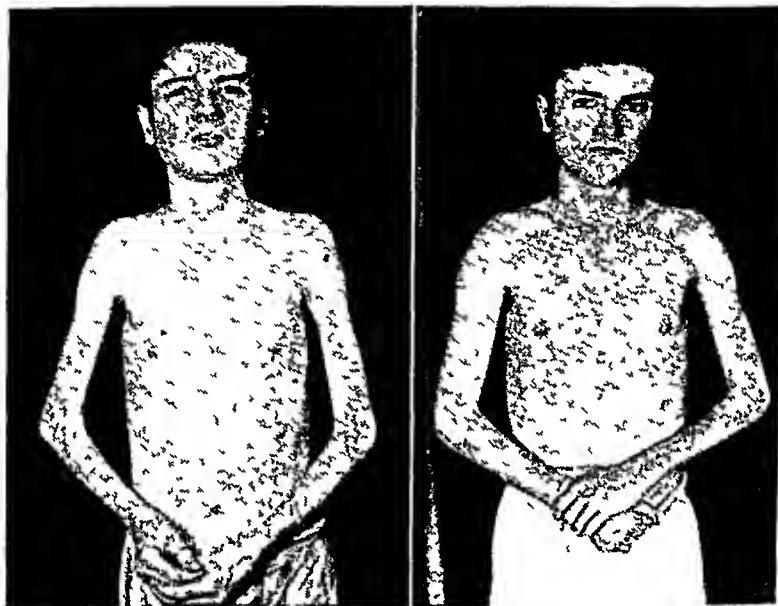
A boy of 14 was first seen at the Lahey Clinic in October 1938, because of tenderness and swelling of the right wrist, which had been present for five days. A long illness had antedated the development of the recent acute condition. At the age of eight, following an injury to his face while riding on a sled, he noted weakness and stiffness in the extremities and discoloration of the skin. A diagnosis of dermatomyositis was made at that time, and physiotherapy was advised. Although the boy was able to be up and around, his muscular activity became greatly reduced so that he could not kneel or completely extend his arms. As time went on, white hard material was deposited in the skin and subcutaneous tissue over the arms, legs and trunk. The skin over these deposits occasionally broke, and thick, chalky material drained. It was in the region of one of these deposits that the tenderness and swelling developed which brought the boy to the clinic.

Physical examination showed that the patient was fairly well developed, but moderately undernourished (figure 1). He weighed 98 pounds. The pulse and blood pressure were within normal limits. The skin of the face was mottled, there being linear regions of thickening and atrophy, with some capillary dilatation. The skin over the arms, legs and trunk was slightly erythematous and thickened, with fine scaling. Numerous white superficial nodules, measuring from 2 mm to 1 cm in

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diameter, were present over the arms and legs, and somewhat larger nodules were found over both elbows. The right wrist was red, swollen and intensely tender. The muscles of the forearms and legs were firm and markedly atrophied. The forearms could not be extended beyond a 60 degree angle, nor could the lower leg be flexed on the thigh, the patient thus being unable to kneel. The fingertips and ends of the toes contained superficial plaques similar to those on the forearm. Capillary dilatation was present in the region of the cuticle of the fingernails and toenails.

Examination of the blood revealed the hemoglobin to be 96 per cent, erythrocytes numbered 5,150,000 and leukocytes, 10,300. Urinalysis and the Hinton test gave negative results. The serum calcium, phosphorus and phosphate determinations were all within normal limits.



Oct 1938

Aug 1941

FIG 1 Improvement in general physical condition may be noted. Arms can be flexed to a greater degree than when the patient first came to the clinic.

Roentgenograms of the chest, extremities and abdomen demonstrated multiple, scattered, irregular areas of calcification in the subcutaneous tissue (figure 2). The calcium content of the bone appeared normal.

A specimen of skin and subcutaneous tissue was removed from the region of the right scapula for microscopic study. Localized fibrosis with chronic inflammation and calcification was found.

A diagnosis was made of calcinosis secondary to dermatomyositis, acrodermatitis chronica atrophicans and cellulitis of the right wrist, resulting from infection in a calcium deposit. The infection in the region of the wrist subsided promptly following treatment with continuous warm packs. Treatment aimed at the general disease was then considered. Because of the benefit from a ketogenic diet, reported by Kennedy, the patient was placed on this diet and, in addition, was given 45 grains of ammonium chloride and $\frac{1}{2}$ grain of Armour's desiccated thyroid each day. Lanolin was used locally on the skin.

The patient's course was followed for eight months on this plan of treatment. It was extremely difficult to keep him in ketosis as he did not cooperate well in continuing his diet and took ammonium chloride only periodically. During this time two infections, one on the left foot and one on the elbow, developed, causing considerable



FIG 2 Note absorption of large calcium plaque on anterior aspect of the forearm

pain. In both instances a large amount of chalky substance drained from the infected areas before healing took place. The patient gained seven pounds, but no change took place in the skin or function of the extremities.

Because of the lack of discernible improvement on this regimen, it was decided to employ other therapy. It was at this time that Ramsdell reported his success in a similar case following unilateral parathyroidectomy, and operation was advised for this patient.

Operation was performed August 14, 1939, under cyclopropane ether anesthesia with carbon dioxide absorption technic. Through the usual collar incision, the pre-

thyroid muscles were divided on the right side, exposing the right lobe of the thyroid. After division of the middle thyroid vein, the inferior parathyroid was demonstrated and totally removed. Frozen section demonstrated it to be parathyroid tissue. Following this, the superior pole of the right lobe was mobilized and several bodies suggestive of parathyroid glands were removed. None showed parathyroid tissue. In order to complete the dissection, the upper third of the right lobe of the thyroid was removed. Both superior and inferior thyroid arteries were ligated. The left lobe of the thyroid was not disturbed.

The patient's postoperative course was satisfactory. Although a positive Chvostek sign was elicited after the operation, no subjective symptoms of tetany de-

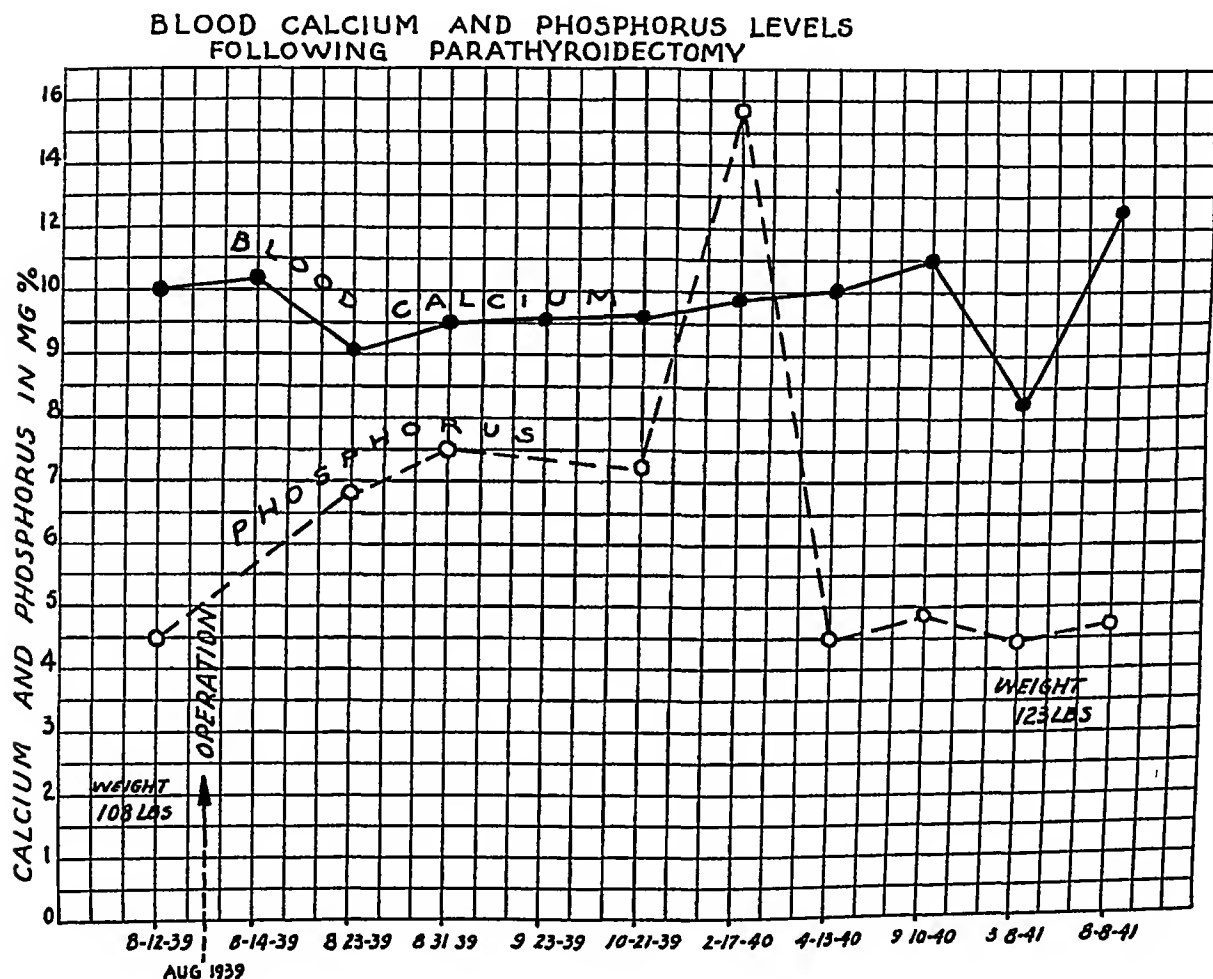


FIG 3

veloped. He was discharged from the hospital five days after operation. The subsequent level of the serum calcium and phosphorus is shown in figure 3. There was a steady gain in weight after the operation so that at the end of eight weeks he had gained seven pounds. Soon after the operation, noticeable loosening of the extremities took place.

Two years have now elapsed since the operation. The patient's general health has markedly improved, he has gained 15 pounds in weight (figure 1). All ulcerated areas have healed, the texture of the skin has improved, and many of the calcium deposits have disappeared. The function of the arms has improved, and the patient can now kneel with ease. The muscles have increased in size and strength. A roent-

genogram (figure 2) shows almost complete absorption of one large calcium deposit on the anterior surface of the forearm. A few deposits are still visible on the posterior aspect.

SUMMARY AND CONCLUSIONS

A boy of 14 was observed who had calcinosis of the subcutaneous tissue and muscles, associated with acrodermatitis chronica atrophicans secondary to dermatomyositis. When the patient was first seen there was marked restriction of the motion of the extremities and infection in the region of the calcium deposits. Treatment with a ketogenic diet, ammonium chloride and desiccated thyroid for one year produced no apparent improvement. At the end of this time, unilateral parathyroidectomy was performed, producing chronic tetany. No subjective symptoms of tetany developed, although a positive Chvostek sign was elicited. The serum phosphorus level became elevated and remained so for a period of eight months, the value for the serum calcium remained normal. During the two years since operation marked improvement has occurred, and roentgenograms demonstrate absorption of some of the calcium deposits. All the skin infections have healed, and the texture of the skin has improved.

The response of the serum calcium and phosphorus in this patient following parathyroidectomy suggests that the parathyroid glands are primarily involved with phosphorus excretion, and therefore account for the increase in the serum phosphorus level. The failure of the serum calcium level to fall may be explained on the basis that the mobilization of calcium from the calcium deposits in the subcutaneous tissue replaces that lost through urinary excretion. As the blood elements have returned to normal, no further clinical improvement is now anticipated.

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MULTIPLE MYELOMA *

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MULTIPLE myeloma is considered a malignant tumor exhibiting multiple foci throughout the red bone marrow in the body. One of the first cases of this disease reported in 1845 by William McIntyre received very little attention from the medical profession. Not until 1882 was it definitely recognized after presentation by Kuhne and it was further described in 1889 by Kahler. The etiology of the disease is as yet unknown. The majority of cases occur in the male between the fourth and sixth decades. In the cases reported, the principal

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symptoms have been pain, tumor, deformity, and fracture, and there may be systemic changes affecting the respiratory and cardiorenal systems and at times the gastrointestinal tract and blood stream.

The pain is frequently intermittent and is generally referred to the back and to the extremities. It is aggravated by movement and increases in intensity as the disease progresses. Periods of remission are not uncommon.

The presence of small tumors distributed over the ribs, sternum, clavicles, spine and extremities are important diagnostic criteria when present. They may

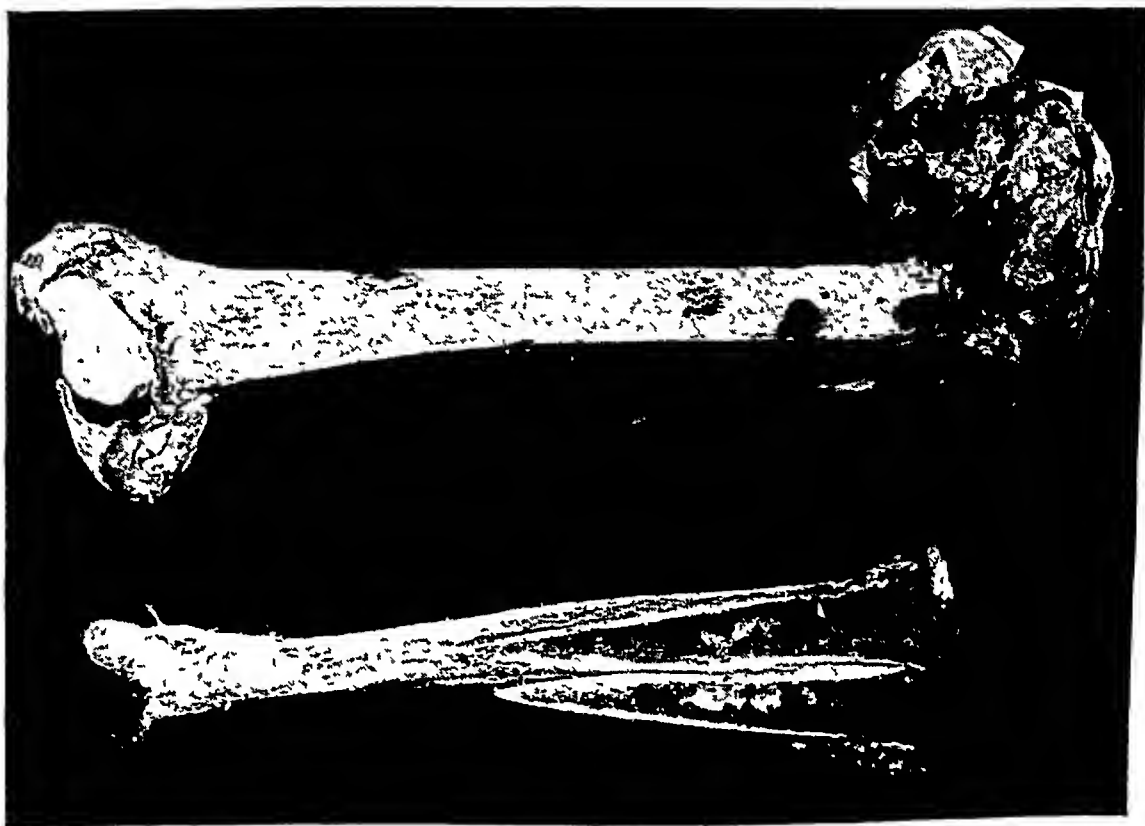


FIG 1 (Above) The rounded head of the femur with collapse of the entire upper end of the femur. (Below) Tibia. This section reveals the diffuse character of the hemorrhage into the tumor and its distention, with thinning of the cortical layer of the shaft.

result in pathological fractures. Neurological manifestations, if present, are the result of compression of the cord by these tumors and may result in paralysis, and in bladder and rectal incontinence which in turn may lead to decubitus ulcers. Kidney changes are not characteristic, but albuminuria is frequently present and the albumin-globulin ratio may be reversed. The blood picture is not characteristic except for a marked anemia. Roentgenologic study of the bones forms the most important diagnostic procedure, although the final diagnosis must be made by microscopic study.

CASE REPORT

This report is of a white male, 25 years of age, who was admitted to the hospital November 13, 1936. He gave a history of having been apparently well until September 1936, at which time he first noticed the development of a dull, ache-like discomfort in

both thighs which felt deep as though it were in the bones, and which were present more often when he was tired. Believing this discomfort to be merely the result of over-exertion, he did nothing about it until August 1937 at which time he went to a chiropractor for therapy, and two months of chiropractic treatment consisting of massage and light did not help to any great extent. From September 1937 until July 1938 he had no treatment at all, but in July 1938 he again began to have severe steady aches which developed in both hip regions and in the lumbosacral spine, and again he sought medical advice. Physiotherapeutic measures were tried until October at which time the pain became more severe and he was unable to continue his work as a steel catcher. The pain was aggravated by bending over or lifting heavy objects, and on occasions the pain was so severe that he fainted. At this same time the patient noted a change in the character of the pain. Whereas previously it had been dull, aching in character, deeply situated, now it became sharp, stabbing, and at times lancinating in character, aggravated by any movement of the lower spine or hips. It was not continuous, however, and when the patient lay perfectly quiet he was fairly comfortable. In October 1938 he found it necessary to use a cane when walking and even then experienced such severe pain in the lower spine, thighs and hips that absolute bed rest was advised and he was referred to the Medical Service for further care.

The patient had had no definite complaints referable to any of the systems of the body other than those already mentioned in reference to his locomotor activity. He had never used alcohol and had been free of venereal disease. He had had the usual childhood diseases. He had had a fracture of the right humerus at 11 years of age, and a fracture of the right ankle at 17 years of age.

The family history was negative for any chronic disease, and his father, mother and 10 siblings were alive and well. He was married, but had no children.

Upon admission to the ward the patient appeared to be a well developed, poorly nourished white male of 25 years, not in acute pain while lying in bed, but expressing a great deal of pain on any attempt at motion for examination. Essential physical findings were as follows: Head: There was no evidence of enlargement, depressions or previous injury. Eyes: The pupils were round, equal, regular, reacted to light and on accommodation. The conjunctivae appeared pale. Fundi were negative. Ears: Both drums were clear with a normal light reflex. Nose: The septum deviated slightly to the right. There were no mucous membrane changes. Mouth: The lips were pale, the tongue protruded in the midline, the mucous membranes were clear. The neck was flaccid, the cervical glands were not palpable. The trachea was in the midline. The chest was equal and symmetrical, fremitus and resonance were not impaired. The breath sounds were vesicular in quality and came through well in all portions of the lungs. The heart: The apex was in the fifth interspace, 8.5 cm from the mid-sternal line. The base was not enlarged to percussion. The heart sounds were regular and of good tone, there were no murmurs. The radial vessels were moderately sclerotic. Blood pressure was 160 mm Hg systolic and 100 mm diastolic. The abdomen was soft and not tender. The liver and spleen were not enlarged. There was no spasm, and no masses were palpable. The genitalia were those of a normal male. The spine was held rigid. There was kyphosis of the lumbar region but no evidences of tumor masses. There were no tender spots elicited on palpation of the spine. Extremities showed no edema.

On admission to the ward the red blood count was 2,290,000 with 56 per cent hemoglobin. The leukocyte count was 9,400, with 49 per cent lymphocytes, 2 per cent monocytes, the remainder in the polymorphonuclear series. The red cells showed moderate variation in size and shape. Three nucleated red cells were noted, diffuse basophilia was present. Color index was 0.9. Subsequent counts showed much variation, between 2,300,000 and 3,200,000 red cells and 4,000 to 9,000 leukocytes. The differential count varied, but in most instances was normal with an

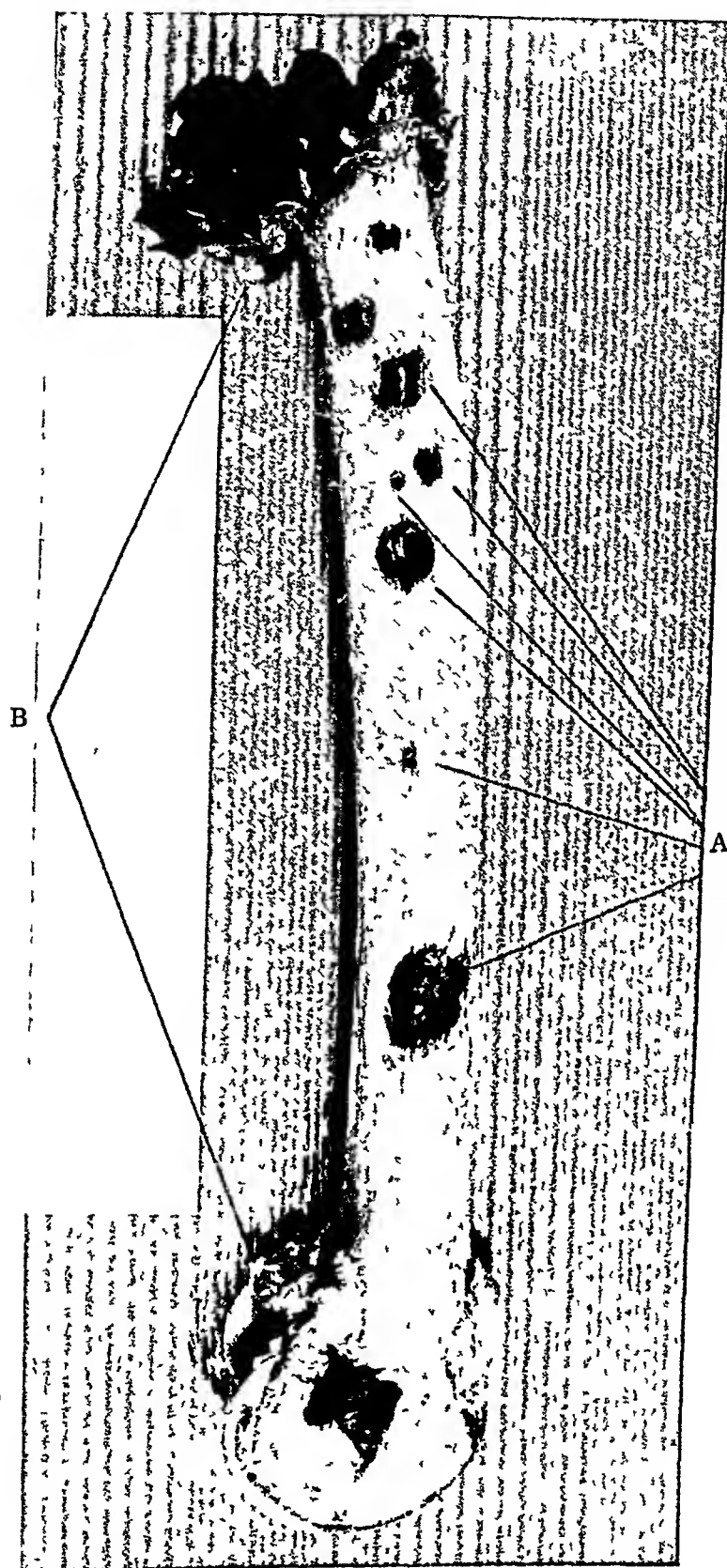


FIG 2 Femur The outlines of the circumscribed tumor nodules, *A*, can be seen on the cortical surface The thin shell-like character is noted at both ends, *B*

occasional relative lymphocytosis. The red cell count was typical of a progressive chronic disease and although at first it showed definite improvement on iron and liver therapy, it soon began to show a gradual decrease in spite of the therapy offered. Approximately one year following his admission his count had dropped to 1,660,000 with 38 per cent hemoglobin and there was a leukopenia of 2,350 with 36 per cent lymphocytes, and 64 per cent polymorphonuclears.

Subsequently only slight and transient improvement was obtained by repeated transfusions, and on March 16, 1940, the red cell count had fallen to 900,000, with 23 per cent, or 3.4 grams of hemoglobin.

Urinalysis done approximately weekly during the patient's stay in the hospital revealed occasionally a trace of albumin or sugar, but as a general rule was negative. Specific gravity varied from 1.010 to 1.015 with an adequate urinary output. The sediment on most occasions was normal. Tests for Bence-Jones protein on 15 occasions were uniformly negative.

Blood chemistry revealed the following data. The blood urea was 12 mg per 100 cc on admission, rose to 18 mg in February 1939, and remained at approximately this figure except for a terminal elevation to 22 mg per 100 cc. The blood sugar varied between 82 and 96 mg. Kidney function tests showed a moderately low specific gravity with satisfactory urinary output as evidenced by the Mosenthal test, whereas phenolsulfonphthalein tests showed kidney impairment with excretion between 45 per cent and 55 per cent of the dye in two hours. On November 20, approximately one week following his admission, the blood calcium level was 13 mg, the inorganic phosphorus 4.3 mg, total proteins were 6.55, albumin 2.82, globulin 3.73, and albumin-globulin ratio 0.72. Phosphatase at this time was 3.2 Bodansky units and ionized calcium, 6.2 mg. The total protein a month after his admission was essentially the same with an albumin-globulin ratio of .76. In November of 1939 the blood calcium was 13.17 mg, the inorganic phosphorus 5.2 mg, approximately three months later the blood calcium was 12.51 mg, the inorganic phosphorus 4.9 mg. In April 1939 the blood calcium was 13 mg, and phosphorus was 4.8 mg. Sedimentation rate done on four occasions showed an approximate average of 14 mm. Blood cholesterol was 174 mg, and blood chlorides 630 mg.

On November 19, 1939 a roentgenogram of the chest showed the lung fields to be clear. The heart and aorta were within normal limits, the diaphragms normal in position and contour. The spine, particularly the lumbar, all pelvic bones, both femurs and humeri, all ribs, scapulae and the skull showed numerous punched out, sharply delineated areas of decreased density, typical of multiple myeloma. Because of this, a rib biopsy was done on December 6, 1938, the material consisting of a fragment of rib 4 cm in length which, when split through, showed a clear, gelatinous-like material in a sharply punched out area. When sectioned these areas showed a profuse proliferation of cells with occasional mitotic figures, that were larger than the small lymphocyte, more nearly approximating a large lymphocyte. Some of these cells showed reticulation of their nuclei, some showed cytoplasmic processes which made a delicate reticulum in which these cells were found. There were also small clusters scattered in and among the cells that were definitely small lymphocytes. None of the normal bone marrow elements could be made out. Occasionally there was a large cell resembling a megakaryocyte. The diagnosis was multiple myeloma.

Roentgen-ray examination repeated in January 1939 revealed a definite progression of the myelomatous lesions in the skull, lumbar spine, pelvic bones and along the shafts of the femur. The forearms, legs, hands and feet showed no evidence of lesions. Roentgenogram of the chest, repeated because of chest complaints, revealed the lung fields clear with no evidence of lung metastasis. In March 1939 again roentgenograms showed marked progression of the myelomatous lesions in the pelvic bones, upper thirds of the femurs, lumbar spine, some in the ribs, skull and humeri.

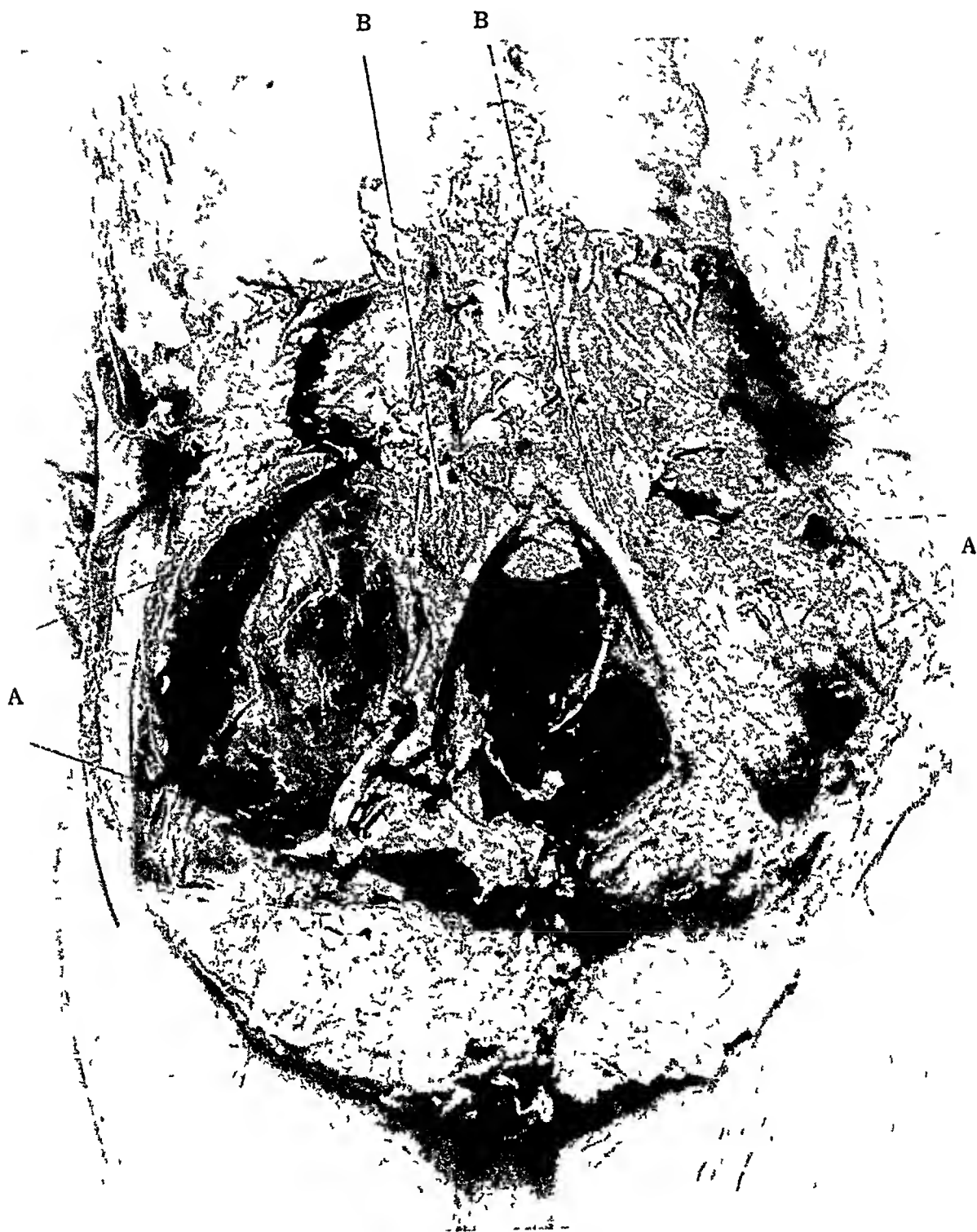


FIG 3 The pelvic picture reveals two large bulges, *A*, one on each side, outlined mesially by the bifurcated aorta, *B*. The mass on the right side has been incised to reveal the diffuse hemorrhagic character of the tumor. The psoas muscle and sciatic nerves as well as the returning veins are stretched and compressed by the bulging. The osseous structure was reduced to sand-like remains.

The course of the case during his stay in the hospital from the time of admission until March 23, 1940 was that of a chronic progressive fatal disease. Because of the severe pain the patient was placed on a hard board mattress but found little relief and was kept as comfortable as possible with narcotics. Therapy for the anemia has already been mentioned and other therapy was purely symptomatic.

In February 1939 he began to exhibit frequency, urgency and incontinence of urine, following which a diagnosis was made of neurogenic dysfunction of the bladder. Antispasmodics were given with some relief.

Dermatologically two complications developed in the course of the disease. In March 1937 herpes zoster was noted, which improved satisfactorily on salicylate treatment and calamine lotion. Two years later there was noted on each shoulder

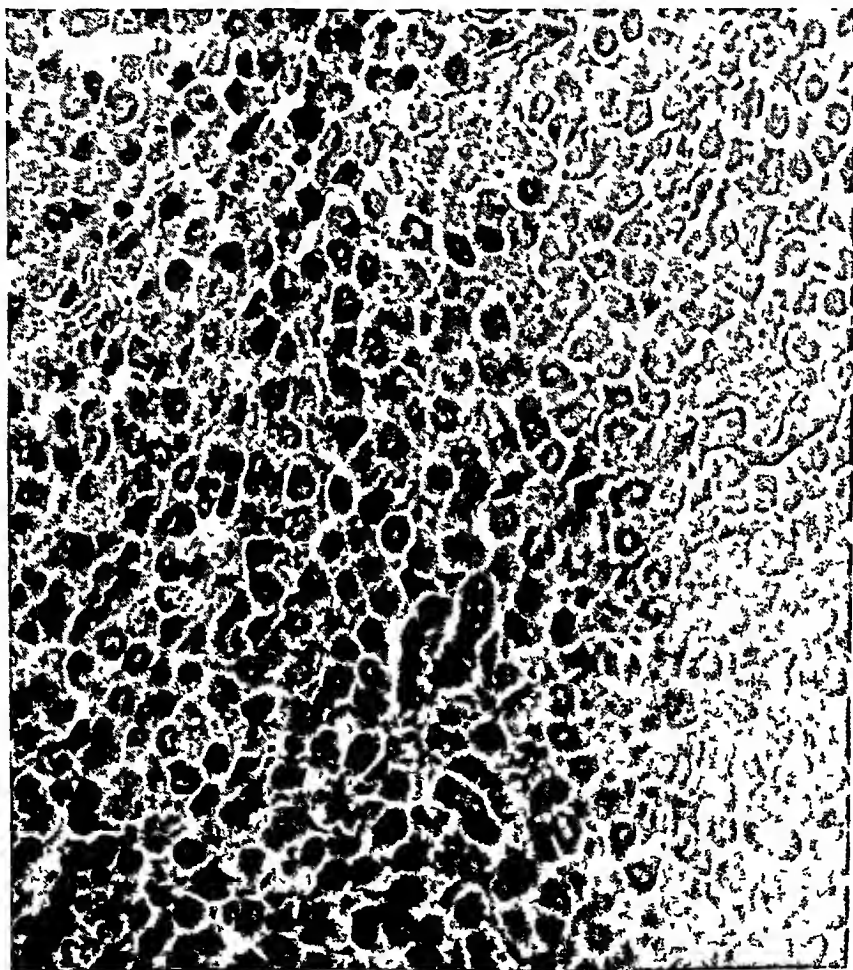


FIG 4 The cell type is not clearly the plasma cell, the pyknotic nucleus appears only at times, then only suggestively, the cytoplasm generally is basophilic, clear or fragmented. The mononuclear cell with definite nuclear membrane, narrow rim of cytoplasm is the more common type. Mitotic figures are few. Diffuse hemorrhage with fibrin dominates the picture, many nucleated reds are present. The breakdown of the osseous trabecula is complete and extends into the cortical layers which are reduced to a thin shell. The latter have been perforated by periosteal invasion that presents either as diffuse masses or extensive infiltrates, e.g. the ribs which are $2\frac{1}{2}$ times the normal diameter. Or the thin cortical layers are tremendously distended with hemorrhage and tumor as in the ilia.

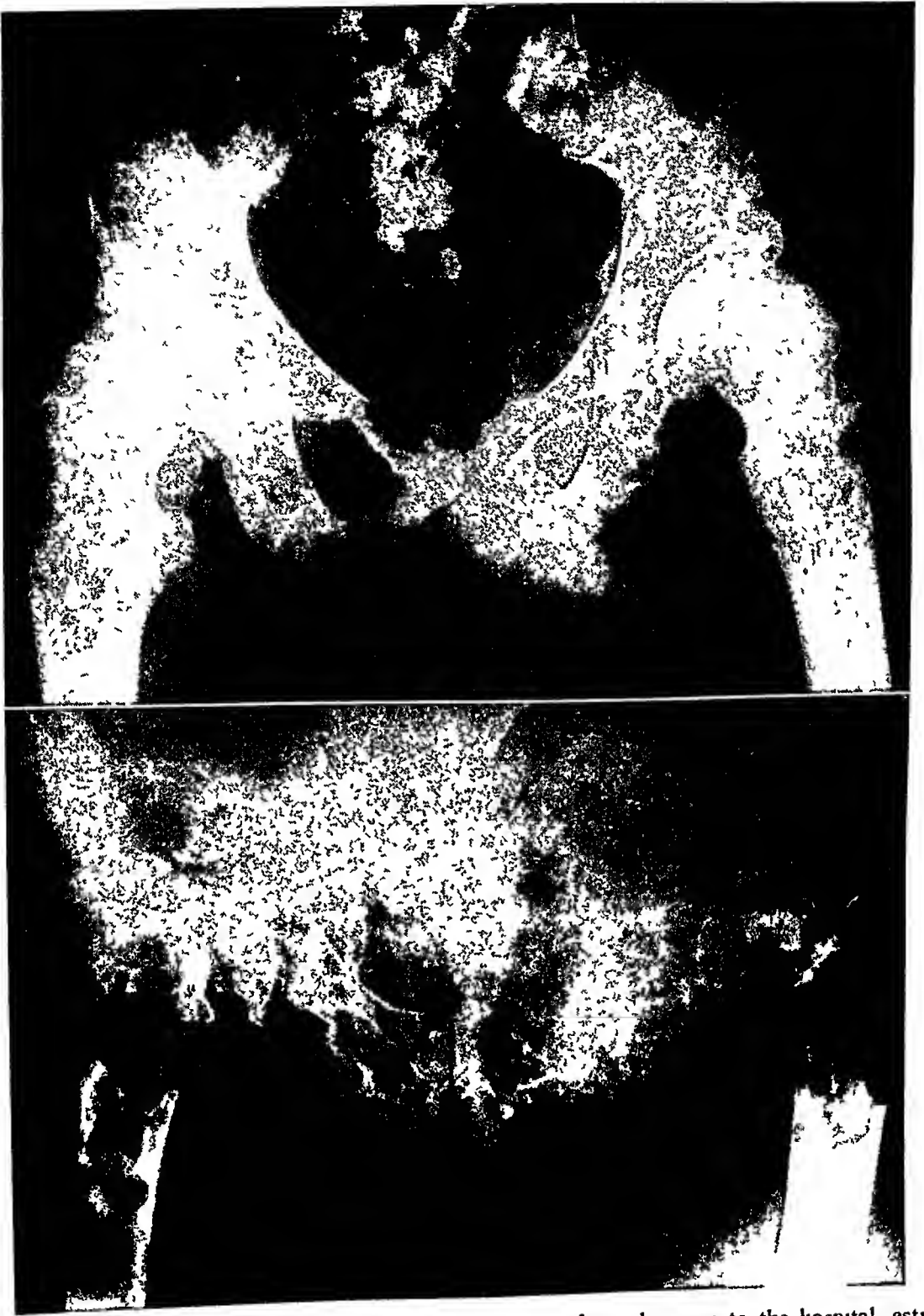


FIG 5 (*Above*) Roentgenogram taken three days after admission to the hospital, estimated to be 18 to 20 months after the onset of the disease. Note the characteristic rounded punched out areas with their evident predilection for the cancellous structures. Even now confluence is in evidence throughout the involved fields. (*Below*) The marked progression of the disease is strikingly demonstrated by comparison with the cut above. Pathological fractures of the pelvis and both hips are now present. Notwithstanding the great increase in size of the lesions, a circumscribed outline is easily seen and helps to differentiate from carcinomatosis.



FIG 6 Owing to the numerous scattered lesions of myeloma the bodies of the first, third, fourth and fifth lumbar vertebrae are compressed. There is also narrowing of the intervertebral spaces, particularly between the third and fourth vertebrae.

posteriorly a palm-sized plaque of infiltration of the cutis, which was confined to the dermis and was moderately tender on pressure and diagnosed as calcinosis cutis.

In October 1939, approximately a year following his admission, he began to show edema of his left leg, which gradually extended upward to involve the penis and scrotum. This seemed to subside somewhat but he never definitely recovered.

In March 1940 his condition became more serious. He began to complain of dyspnea, his respirations were rapid, and his lungs showed bilateral basilar congestion. His heart sounds were poor, the pulse was rapid with a rate of 120 per minute, but no definite bruits were heard. He complained of generalized pain throughout his body.

He died on March 21, 1940 with a final diagnosis of multiple myeloma, marked hypochromic anemia, and circulatory failure

Postmortem examination was made on March 22, 1940. The body was moderately well developed and nourished, but the extremities, especially the lower ones, lacked tone, were flaccid and semiflaccid. The skin surface was shiny. There was an increase in the lateral diameter of all extremities. The bones of the knee and hip joints were friable and compressible with a fine crackling crepitus on palpation. The soft tissues were edematous. Postmortem lividity and rigidity were present.

The ribs were mottled and callous and there were soft reddish bulges from the softened areas. The pleura was smooth and glistening. The lungs were voluminous, grayish-pink and dark gray. Crepitus was absent throughout. Cut sections showed the same mixed coloration with a marked pouring out of thin serous froth from the cut surface.

The pericardium was smooth and glistening, the heart was normal in size, the muscle was pale and flabby. The valves and orifices were clear. The left ventricle was three times as thick as the right. Coronary vessels were patent. The aorta was thin and showed wrinkling and yellowish plaques on its intimal surface.

Gastrointestinal. The esophagus was not remarkable. The pylorus was contracted, the duodenum small, the large intestine not remarkable.

The liver was slightly reduced in size with a smooth capsule. The spleen was approximately three times normal in size, its color diffuse bloody red. The adrenal glands were of normal size. The gall-bladder was thin walled and contained 20 c.c. of dark inspissated bile.

Both kidneys were slightly smaller than normal, the capsule was thin and stripped easily, revealing a smooth surface. In the cortical portion in the columns of Bertini there were noted slight streakings, following especially the lines of the straight tubules, which proved to be calcium deposits due to a high blood calcium during his life. The pelves and ureters were clear, the bladder small. The prostate gland was normal in size.

Skeletal system. All the bones were involved to a lesser or greater degree by the tumor, especially the long bones. On opening the left femur the left hip joint was found to be completely disintegrated, and the myeloma had destroyed the osseous structure and invaded the soft tissues. Similarly, in the pelvis, both ilia were massive, larger than grapefruit size, bulging forward and upward, compressing the vessels and the lumbosacral nerves, so that venous circulation was retarded, resulting in edema. These masses on dissection were hemorrhagic, consisting of fat, and bony spicules, being completely disintegrated. The remainder of the femur showed circumscribed areas varying in size. The lower end of the femur and the upper end of the tibia were completely broken down. Both tibiae showed mottling and points of perforation by the myeloma. The vertebral column was similarly involved. Permission to examine the cranium was not obtained.

The skin showed circumscribed, hard, pale plaques which on section proved to contain calcium.

The final anatomical diagnosis, which was in accord with the clinical impression, was (1) Multiple myeloma with hemorrhages, bone absorption and multiple fractures, (2) marked secondary anemia, (3) metastatic calcification of kidneys and skin, (4) myocardial degeneration and dilatation, (5) pulmonary edema.

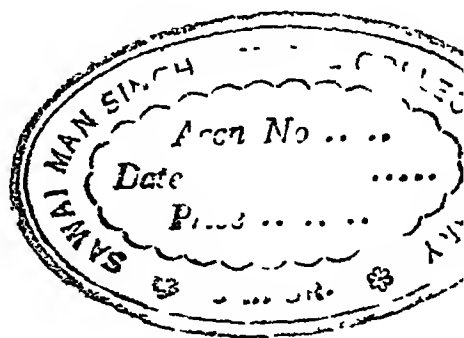
SUMMARY

It is of interest that although red cell regeneration was active, the anemia was pronounced. Another feature of interest was the complete loss of osseous structural support that exists in the normal skeletal frame. The body as a

whole seemed like a fluctuant mass, flattened and collapsed, each handling was productive of further disruption of continuity of the osseous structure. Another point of interest was the edema of the lower extremities, which was readily accounted for by the obstruction to the venous return produced by the pelvic masses.

We have, then, a case of multiple myeloma of approximately four years' duration observed in a young male 25 years of age. He shows the characteristic history of vague pains gradually becoming more severe, and involving chiefly the lower spine and lower extremities. The laboratory data in this case were, for the most part, in accord with the usual findings, except that Bence-Jones protein could not be demonstrated in the urine although examined on approximately 15 occasions. A high blood pressure was repeatedly observed, as a result of calcium deposit in the kidney. The clinical course and laboratory data were in accord with those usually reported in this disease.

We are indebted to Dr. William F. Jacobs, pathologist of the Edward J. Meyer Memorial Hospital, for the pathologic report in this case, and to Dr. Clifford R. Orr for the roentgenologic studies.



EDITORIAL

THE WAR AND MEDICAL EDUCATION

ALTHOUGH our country has been at war less than a year, extensive changes in medical education have already been instituted in order to meet special conditions created by the immediate needs of our armed forces. These changes are both quantitative and qualitative in character.

The principal quantitative change that has been put into effect is the adoption by the majority of medical schools of an accelerated program whereby the medical course is shortened from four to three calendar years. This means that the four academic years can now be completed within three calendar years by continuous instruction throughout the summer months at the sacrifice of the lengthy summer vacations so welcome to students and faculty alike in peacetime. There has been no reduction in the total number of hours devoted to instruction in the medical sciences—in other words, no lowering of the standards of the medical school or of the requirements for the degree of Doctor of Medicine. Since the majority of colleges that offer premedical courses have also adopted an accelerated program, it is now possible for a student to obtain the A B or B S degree in three calendar years and the M D degree in three more calendar years, a total of six years of undergraduate and professional education as against the eight years previously required for such an accomplishment.

As a result of the accelerated program, medical schools will graduate a full class every nine months. These graduates will be eligible for service with the army or navy medical corps as soon as they have completed a nine to twelve months internship. Hospitals have changed their dates for internships to dovetail with the graduation dates of the accelerated medical schools. Such a speeding up of medical education should prove an important factor in keeping our armed forces supplied with a steady stream of vigorous young medical officers, well prepared for active duty in each and every theater of the war.

The accelerated program has been subjected to certain unfavorable criticism. It is undoubtedly true, as many have alleged, that the students may be less alert and "grow stale" under the pressure of almost continuous instruction without benefit of a long summer vacation in which to "digest" the learning that they have imbibed during the previous academic year. This necessarily unfortunate state of affairs is more than offset by the sense of satisfaction on the part of the students that they are wasting no time in preparing themselves to "get in the thick of the fight." A good many medical students find it difficult to justify to themselves staying on in school when a large number of their non-professional contemporaries are already on active duty with the armed forces. Surely, it must be some consolation to them to

know that the Army and Navy regard our medical schools in much the same light as West Point and Annapolis, that is as training grounds for future officers

To those medical students of limited means the accelerated program has presented an acute financial problem. Tuition bills must be met more frequently, yet there is no longer the opportunity to earn money during the summer months with which to help defray expenses. Loan and scholarship funds have been established by the United States Government and by the Kellogg Foundation in order to meet just such an exigency. The medical schools, themselves, can do their part by offering more scholarships, raising loan funds, and granting deferment of tuition in special cases.

Coincident with the adoption of the accelerated program, medical schools have been obliged to strip their faculties down to a skeleton force of "essential" instructors in order to release as many physicians, surgeons and scientific specialists as possible for service with the armed forces. Thus a relatively small staff must assume the responsibility of carrying the full load of the year-around teaching schedule and wartime research. In addition to the instruction of medical students, these depleted faculties will be expected to offer refresher courses, in subjects of military importance to medical officers of the Army and Navy. We may confidently expect that all those instructors who have been prevented from joining the armed forces of the nation, either through physical defects or through their "essentialness" to their medical schools, will shoulder these added teaching burdens with wholehearted enthusiasm as their contribution to the war effort. Full-time men must expect to work longer hours and to subjugate their own research interests to the immediate demands upon their time, while part-time instructors should and undoubtedly will devote a larger portion of their time to teaching in spite of the increase in their private practice resulting from the shortage of physicians remaining in civilian practice.

The Selective Service status of medical and premedical students raises a number of problems of considerable interest. Under the original Selective Service Act, a recommendation was issued to local draft boards that all medical students in good standing be classified II-A—that is, deferment for occupational reasons. More recently, medical students have been permitted to apply for reserve commissions as second lieutenant in the Medical Administrative Corps of the Army or as ensign (H V P) in the Medical Reserve Corps of the Navy. Such a tentative appointment protects a medical student from being drafted throughout his medical school career and a one-year internship, after the completion of which he is subject to call for active duty as first lieutenant in the Army Medical Corps or lieutenant (j g) in the Navy Medical Corps. Medical schools have been requested not to ask draft deferment for students who have failed to make application for such a reserve commission. Premedical students who have been admitted to a Grade A medical school may apply for similar commissions, provided that they expect to enter medical school within one year. The opportunities afforded

by such legislation have served to prevent all medical students and the majority of premedical students from being drafted up to the present time. However, if the lower draft age limit is dropped to 18 years, it is obvious that further measures should be forthcoming. We could scarcely expect the medical schools of the country to admit students on the basis of their accomplishments in high school or during their freshman year at college. Government provision would have to be made for protecting bona fide premedical students from being drafted, possibly on the basis of a certificate from the dean of the college. Otherwise, medical schools would be obliged to close their doors for lack of a student body.

Qualitative changes in the curriculum of medical schools have been designed to emphasize in particular traumatic surgery, diseases of young adults, and infectious diseases prevailing in the various countries and climates to which our armed forces may be exposed. Every medical student should become thoroughly familiar with such infections as influenza, pneumonia, meningitis, rheumatic fever, syphilis, gonorrhea, chancroid, the dysenteries, enteric fever, typhus, malaria, and tropical diseases rarely encountered in this country such as yellow fever, kala-azar, dengue, Australian "Q" disease, and a variety of others. He must be drilled in the proper technic of debridement of wounds, the treatment of burns and shock, and chemotherapy with the sulfonamide drugs. In order to attain such a goal, additional time must be allotted for practical training of the students in the accident room, the dermatologic and venereal disease clinics, and the contagious disease wards, and lectures in tropical medicine by competent authorities are being arranged. In addition, first year students should be given an intensive course in first aid shortly after they enter medical school in order that they may do their bit intelligently, should this country be subjected to bombing raids. For the same reason, every practicing physician should complete a refresher course in first aid in order that he may be better prepared in case of enemy raids in his vicinity.

Lastly, it is obvious that organized post-graduate instruction of physicians remaining in civilian practice must of necessity be sharply curtailed for the duration of war. There are two clear-cut reasons for this: (1) the medical officers of the Army and Navy must be given first consideration in post-graduate teaching, (2) owing to the shortage of physicians left in private practice, it will be almost impossible for any individual to take time off from his duties at home to devote to post-graduate courses.

We have attempted to enumerate the major changes in medical education that have been brought about by the war. It is quite apparent that every man and woman connected in any way with medical education may expect to work harder and longer hours. Americans at Bataan, Wake, the Coral Sea, Midway, the Solomons, and Dieppe have more than done their part. It is utterly unthinkable that we of the medical profession could let them down!

W. H. B

REVIEWS

Psychiatry in Medical Education By FRANKLIN G EBAUGH, M D, and CHARLES A RYMER, M D With Foreword by Dr Adolf Meyer 619 pages, 24 X 16 cm The Commonwealth Fund, New York 1942 Price, \$3 50

This book will be of chief interest to psychiatric teachers in our medical colleges, although it would well repay study by medical educators in general, by psychiatrists who are interested in the present status and in the future of their specialty, and by young physicians who are interested in taking up psychiatry as a specialty. It represents an enormous amount of work in collecting a large number of facts. Much of this information was collected directly by the senior author.

The first section of the book concerns itself with general psychiatric ideology. I can recommend the chapter on Psychobiology to anyone to whom this is a more or less meaningless word. It contains one of the most lucid explanations of what psychobiology means that has so far appeared. This is followed by a careful survey of instruction offered in psychiatry in all Class-A medical schools in the United States and Canada. It is full of detail as to variations in courses and attitudes in the various schools. It winds up with a chapter on the opportunities for psychiatric education and some detailed and helpful suggestions for setting up psychiatric services in general hospitals, pointing out the great need for such services, their feasibility and usefulness to the general hospital especially in those localities where for various reasons it is not practical to establish a separate psychiatric unit, and incidentally, points out that financially such a service not only maintains itself but should add a pleasant return to the hospital's income. The next section has to do with graduate and post-graduate training in Psychiatry and does not seem quite as adequate as the other sections, but again contains a great deal of useful information as to procedure in obtaining such training and about what the candidate may expect. The last section of the book has to do with prospects for psychiatric development in the near future and a review as to what seems a desirable psychiatric curriculum in our medical schools.

The appendices take up the methods by which the information was obtained and samples of examination and case study technic as used in some of our better psychiatric centers.

I am afraid the field of the book is extremely limited. Within this field it should fill a very definite need.

H M M

Clinical Cardiology By WILLIAM DRESSLER, M D 692 pages, 24 X 16 5 cm Paul B Hoeber, Inc, New York 1942 Price, \$7 50

Students and practitioners will find this book a useful guide to a better understanding of cardiovascular diseases. The author's intention to stress clinical methods and bedside diagnosis is effectively accomplished. The descriptions of physical signs and methods of examination are worthwhile and the attention to diagnostic aids in obscure cases is valuable. For the most part the material is well presented and in agreement with accepted beliefs. By omitting references to the literature the author has achieved better continuity of the text, and one is able to follow the subject matter with a minimum of effort.

The outstanding weakness of the book is in the organization. One finds in Part II discussions of pulsatory phenomena which might better have been included with other physical signs in Part I. The greatest need for rearrangement is in Part III.

where it would be preferable to have chapters in orderly sequence according to etiology. The subject of coronary disease would be clearer if all features were presented in one chapter, and such items as pulmonary regurgitation and arteriovenous fistula should be considered with other subjects of related etiology rather than in isolated chapters. Peripheral circulatory failure and pulmonary infarction deserve fuller discussion. Improvement in organization would make the very valuable contents of this book more accessible to the reader.

C E L

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Pediatrics Vol I Edited by ADOLPH G. DeSANCTIS, M.D. 306 pages, 23.5 × 16 cm 1942 Interscience Publishers, Inc., New York Price, \$4.50

Formulary and Handbook The Johns Hopkins Hospital Edited by JOHN C. KRANTZ, JR. 253 pages, 17.5 × 11.5 cm 1942 John D. Lucas Co., Baltimore Price, \$2.00

Roentgen Treatment of Diseases of the Nervous System By CORNELIUS G. DYKE, M.D., F.A.C.R., and LEO M. DAVIDOFF, M.D., F.A.C.S. 198 pages, 24 × 15.5 cm 1942 Lea and Febiger, Philadelphia Price, \$3.25

Medical Applications of the Short Wave Current Second Edition By WILLIAM BIERMAN, M.D. With a Chapter on Physical and Technical Aspects by Myron M. Schwarzschild, M.A. 344 pages, 23.5 × 16 cm 1942 Williams and Wilkins Co., Baltimore Price, \$5.00

Introduction to Parasitology By A. S. PEARSE, Professor of Zoology, Duke University 357 pages, 23 × 14.5 cm 1942 Charles C. Thomas, Springfield, Illinois Price, \$3.75

A Short History of Cardiology By JAMES B. HERRICK, M.D. 258 pages, 23 × 15 cm 1942 Charles C. Thomas, Springfield, Illinois Price, \$3.50

A Curriculum for Schools of Medical Technology Second Edition, revised By ISRAEL DAVIDSOHN, M.D. 47 pages, 28 × 21.5 cm 1942 Registry of Medical Technologists of the American Society of Clinical Pathologists, Ball Memorial Hospital, Muncie, Indiana Price, \$1.75

Medical Progress Annual Vol III By ROBERT N. NYE, M.D. 678 pages, 24 × 16 cm 1942 Charles C. Thomas, Springfield, Illinois Price, \$5.00

Human Pathology Sixth Edition By HOWARD T. KARSNER, M.D. 817 pages, 26 × 18.5 cm 1942 J. B. Lippincott Co., Philadelphia Price, \$10.00

First Aid—Surgical and Medical By WARREN H. COLE, M.D., F.A.C.S., and CHARLES B. PUESTOW, B.S., M.S., M.D., Ph.D., F.A.C.S. 351 pages, 22 × 15 cm 1942 D. Appleton-Century Co., Inc., New York Price, \$3.00

COLLEGE NEWS NOTES

MORE A C P MEMBERS SERVING IN THE ARMED FORCES

Below appear the names of fifty-four additional members of the College who are serving in the armed forces of their country. Published in the July number of this journal were the names of 667, in the September number 147, and in the October number 105, making a total reported to date (October 8, 1942) of 973, more than 20 per cent of the College membership of 4,808, Masters, Fellows and Associates combined. This number on active military service from the College is especially impressive when it is remembered the average age of members of the College is definitely much higher than the average age of physicians at large. Six members of the College have already been reported "missing in action."

Ellery G. Allen
Benjamin Ashe

Frederick R. Bailey
Gerald A. Beatty
William G. Bernhard
Michael Bernreiter
James M. Bethea
Theodore L. Bliss
James M. Bowers

Richard R. Dalrymple
Perk L. Davis
Frank S. Dietrich
Mark S. Dougherty, Jr.
Thomas J. Dry

Donald R. Ferguson
Robert F. Foster
Joseph J. Furlong

Cleo R. Gatley
William H. Gordon
James R. Gudger

James A. Halsted
Joseph M. Hayman, Jr.
William R. Hewitt
W. Paul Holbrook
William L. Howell

Louis Jaffe

Newton A. Kilgore, Jr.
John T. King

Robert L. King
Phillip T. Knies

Frederick Lemere

George G. Martin
Marsh McCall
Sylvester McGinn
Richard M. McKean
Samuel Morrison

Robert Clinton Page
Robert Collier Page
*Robert T. Phillips
Harry H. Pote

John A. Reisinger
George P. Robb
Max H. Rosenblum

Edward W. Schoenheit
Howard B. Sprague
Harold Sugarman

Myer Teitelbaum
John W. Torbett, Jr.
Wilmot C. Townsend

Neville T. Ussher

Samuel A. Vogel

Robert J. Williams
Olin G. Wilson
Alfred M. Wolfe

* Missing in action

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members

Reprints

Dr Archie H Beard, F A C P, Minneapolis, Minn —4 reprints,
 Dr Nathan Blumberg, F A C P, Philadelphia, Pa —1 reprint,
 Dr J Bailey Carter, F A C P, Chicago, Ill —1 reprint,
 Dr Guy H Faget, F A C P, Carville, La —1 reprint,
 Dr James M Flynn, F A C P, Rochester, N Y —1 reprint,
 Dr Hyman I Goldstein (Associate), Camden, N J —1 reprint,
 Dr Wybren Hiemstra, F A C P, Warren, Pa —1 reprint,
 Dr Charles E Lyght, F A C P, Northfield, Minn —1 reprint,
 Bert E Mulvey, F A C P, Major, (MC), U S Army —1 reprint,
 Robert Collier Page (Associate), Captain, (MC), U S Army —1 reprint,
 Dr Franklin B Peck, F A C P, Indianapolis, Ind —1 reprint,
 Dr Meyer S Rednick, F A C P, Ossining, N Y —1 reprint,
 Dr Lea A Riely, F A C P, Oklahoma City, Okla —1 reprint,
 Dr Leon Schiff, F A C P, Cincinnati, Ohio —1 reprint,
 Dr Henry A Tadgell (Associate), Boston, Mass —3 reprints

AMERICAN COLLEGE OF PHYSICIANS TO EXTEND ITS ACTIVITIES

With the development of the war situation, the Board of Regents of the College will sponsor an extension of regional scientific and social meetings, and will ask the Advisory Committee on Postgraduate Courses to formulate an extended scientific program not only for the College membership, but postgraduate seminars for Army and Navy physicians

On October 20, 21 and 22, the College conducted a series of "Postgraduate Nights" for the naval medical personnel of the U S Naval Hospital, Philadelphia, extending the invitation to all medical officers of the armed forces, to physicians anticipating early entry on active duty and to members of the College. The program was prepared by Dr Thomas M McMillan, F A C P, Philadelphia, in collaboration with Lt Comdr Edward L Bortz, F A C P, Chairman of the Advisory Committee on Postgraduate Courses of the College and College Governor for Eastern Pennsylvania, with Captain Richard H Laning, Commanding Officer of the U S Naval Hospital, Philadelphia, and with Lt Comdr Gordon B Tayloe, Chief of Medicine at the same institution, the program being as follows

Tuesday, October 20, 1942

8 00 p m

GASTRO-INTESTINAL PROBLEMS

"A Classification of Chronic Diarrhea A Discussion of the Alvine Bloody Fluxes" Henry L Bockus, M D, F A C P, Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, Philadelphia

"Recent Advances in Our Knowledge of Small Bowel Diseases" Charles L Brown, M D, F A C P, Professor of Medicine and Head of Department of Medicine, Temple University School of Medicine, Philadelphia, Pa

"Functional Gastro-intestinal Disturbances" Joseph C Yaskin, M D (by invitation), Professor of Neurology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa

Wednesday, October 21, 1942

8 00 p m

BLOOD STUDIES

"Toxic Effects of the Sulfonamides on the Blood" Harrison F Flippin, M D, F A C P, Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa

"Importance of Blood Examination in Certain Tropical Diseases" W Harding Kneedler, M D (by invitation), Associate in Medicine, Jefferson Medical College, Philadelphia, Pa

"The Management of Purpura" George E Farrar, Jr, M D, F A C P, Assistant Professor of Medicine, Temple University School of Medicine, Philadelphia, Pa

Thursday, October 22, 1942

8 00 p m

SOME OF THE MEDICAL ASPECTS OF TRAUMA

"The Crush Syndrome and Burns" Walter Estell Lee, M D, F A C S (by invitation), Professor of Surgery, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa

"Problems of Fluid Balance in the Traumatized Patient" Jonathan E Rhoads, M D (by invitation), Associate in Surgery, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa

"Post-Transfusion Reactions (Blood, Serum and Plasma)" Max Strumia, M D (by invitation), Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa

The Fifth Annual Round-Up, or Regional Meeting, October 23, for members of the College of Eastern Pennsylvania culminated the program with a buffet luncheon at the College Headquarters in Philadelphia, followed by a scientific program at the U S Naval Hospital, Philadelphia, and an evening dinner-meeting addressed by Rear Admiral Ross T McIntire, M D, F A C P, the Surgeon General of the U S Navy. The afternoon program was as follows:

Auditorium, U S Naval Hospital

1 "35 mm Films in the Diagnosis of Chest Conditions" Edmund C Boots, M D, F A C P, Medical Supervisor, School Health Service, Pittsburgh Board of Public Education, Associate Staff, Columbia Hospital, Pittsburgh, Pa

2 "Carcinoma of the Lung" Ferdinand Fetter, M D, F A C P, Lieutenant Commander, Medical Corps, U S Naval Reserve, Associate in Medicine, University of Pennsylvania School of Medicine

3 "Management of Liver Disease" William S McCann, M D, F A C P, Dewey Professor of Medicine, University of Rochester School of Medicine, Physician-in-Chief, Strong Memorial and Rochester Municipal Hospitals, Rochester, N Y

4 "Fever Therapy" Gordon B Tayloe, M D, Lieutenant Commander, Medical Corps, U S Navy, Chief of Medicine, U S Naval Hospital, Philadelphia, Pa

5 "Peptic Ulcer in the U S Navy" Victor W Logan, M D, F A C P, Lieutenant Commander, Medical Corps, U S Naval Reserve, Assistant Attending Physician and Gastro-enterologist in Outpatient Department, Roosevelt Hospital New York City

6 "Neurotic Reaction in War" F H Lewey, M D, Professor of Neurophysiology, University of Pennsylvania School of Medicine, Professor of Neuropathology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa

At the evening meeting, among the distinguished guests were Dr James E Paullin, F A C P, President of the College, Atlanta, Ga, Dr Ernest E Irons, F A C P, President-Elect of the College, Chicago, Ill, Dr William B Breed, F A C P, Chairman of the Board of Governors of the College, Boston, Mass, Capt Robert E Duncan, F A C P, U S Naval Medical Center, Bethesda, Md, Capt A H Allen, Executive Officer, U S Naval Hospital, Philadelphia, Pa, the College Governors for several surrounding States, Executive Officers of the Philadelphia County Medical Society and the College of Physicians of Philadelphia, the Philadelphia Director of Public Health, Dr Hubley R Owen, and the Coroner for Philadelphia, Dr Herbert Goddard. Also present were the Deans of the six medical schools in Philadelphia. Members of the College were in attendance not only from the Eastern Pennsylvania district, but from Western Pennsylvania, New Jersey, New York, Delaware, Maryland, the District of Columbia and from some other more distant points

ACTING GOVERNORS OF THE COLLEGE APPOINTED FOR IDAHO AND MARYLAND

Due to active military service by Dr Louis Krause, College Governor for Maryland, the Executive Committee of the Board of Regents has appointed Dr Wetherbee Fort, F A C P, of Baltimore, as the Acting Governor for Maryland during Dr Krause's absence and inability to serve

Dr Charles Henry Sprague, College Governor for Idaho, has accepted a full-time administrative appointment with the American College of Surgeons in Chicago, and Dr Samuel M Poindexter, F A C P, Boise, has been appointed by the Executive Committee of the Board of Regents as Acting Governor for Idaho

ANNUAL FALL MEETINGS OF THE COMMITTEES AND REGENTS OF THE COLLEGE

The annual meetings of the several committees and of the Board of Regents of the American College of Physicians will be held at the College Headquarters in Philadelphia, December 12-13, 1942. It is at this meeting that the great bulk of College business is transacted, including the consideration of candidates for Associateship and for Fellowship. All proposals for membership must be submitted at least thirty days in advance of action. The next succeeding meeting of the Committee on Credentials will probably be held in March or April, 1943

At a meeting of the Rock County (Wis) Medical Society, September 22, in Beloit, Dr M Meredith Baumgartner (Associate), Janesville, spoke on "Hyperchronic Anemias" and Dr Vincent W Koch, F A C P, Janesville, spoke on "Purpuras and Hemolytic Anemias"

Dr Herbert T Kelly, F A C P, Philadelphia, Pa, presented a paper entitled "What Lies Ahead for the Physician in Nutrition" at a meeting of the Pennsylvania Nutrition Council in Harrisburg, September 18, 1942. Dr. Kelly has been elected Honorary Chairman of the Council for the year 1942-43

Dr Aaron E Parsonnet, F A C P, Newark, N J, addressed the medical staff of the Station Hospital at Fort Dix, N J, on Wednesday, September 30, on "The DaCosta Syndrome"

Dr Richard M Burke, F A C P, Superintendent of the Western Oklahoma Tuberculosis Sanatorium, Clinton, Okla, has resigned. He plans to enter private practice in Oklahoma City

The Third Annual Medical Meeting of the National Foundation for Infantile Paralysis will be held in New York, N Y, December 3-4, 1942

Dr Henry B Mulholland, F A C P, has been appointed Assistant Dean of the University of Virginia Department of Medicine

Dr J Edwin Wood, F A C P, Acting College Governor for Virginia, University, addressed the James River Medical Society in Scottsville, Va, July 15. Dr Wood discussed the use of certain drugs in heart disease

Dr Tom D Spies, F A C P, has accepted the invitation of the Medical Advisory Board of the Hillman Hospital, Birmingham, Ala, and the Jefferson County Commission to continue his experimental work in vitamin research at the Hillman Hospital for at least another year

The Indiana State Medical Association held its 93rd Annual Session at French Lick, September 29-October 1. Among the guest speakers were

Dr Norman H Plummer, F A C P, New York, N Y—"Treatment of Pneumonia",

Dr Lester R Dragstedt, F A C P, Chicago, Ill—"Some Physiologic Principles in Surgery of the Pancreas",

Dr Arlie R Barnes, F A C P, Rochester, Minn—"Heart Disease"

Dr James E Paullin, F A C P, President of the College, Atlanta, Ga, spoke on "American Medicine in the Present Emergency" at the annual banquet of the Association, September 30

Dr Morris Flexner, F A C P, and Dr Max L Garon, F A C P, both of Louisville, presented a paper on "Virus Pneumonia" at the recent annual meeting of the Kentucky State Medical Association

The 75th Annual Meeting of the Michigan State Medical Society was held in Grand Rapids, September 23-25, 1942. Among the guest speakers were

- Dr John A Toomey, F A C P, Cleveland, Ohio—"Chemotherapy in Childhood",
 Dr Harrison F Flippin, F A C P, Philadelphia, Pa—"Sulfonamide Therapy in General Practice",
 Dr Roy W Scott, F A C P, Cleveland, Ohio—"Clinical Aspects of Arteriosclerosis",
 Dr Elmer L Sevringhaus, F A C P, Madison, Wis—"Diagnostic and Therapeutic Problems of Obesity",
 Dr John B Youmans, F A C P, Nashville, Tenn—"The Clinical Importance of Protein in the Diet",
 Dr James Burns Amberson, Jr, F A C P, New York, N Y—"Clinical Interpretation of Early Tuberculosis",
 Dr Irvine H Page (Associate), Indianapolis, Ind—"The Nature and Experimental Treatment of Hypertension"
 Dr Charles F McKhann, F A C P, Ann Arbor, participated in a round table discussion on "Poliomyelitis"

George F Lull, F A C P, Colonel, (MC), U S Army, delivered the Biddle Oration of the Society, September 23 Col Lull spoke on "Résumé of Military Medical Personnel Problems in the Army"

Dr Harold G Wolff, F A C P, New York, N Y, has been named neurologist in charge of a pavilion of twenty-nine beds at the New York Hospital for the study and treatment of neurologic cases

The Medical Society of the State of Pennsylvania held its 92nd Annual Session in Pittsburgh, October 5-8 Among the guest speakers were

- George R Callender, F A C P, Colonel, (MC), U S Army—"Wound Ballistics",
 Dr John H Foulger, F A C P, Wilmington, Del—"Important Factors in Industrial Preventive Medicine",
 Dr Russell L Haden, F A C P, Cleveland, Ohio—"Intravenous Therapy"
 Dr Augustus S Kech, F A C P, Altoona, was chosen President-Elect and Dr Truman G Schnabel, F A C P, Philadelphia, was named Speaker of the House of Delegates

James B Collip, F A C P, Montreal, Que, has been elected President of the Royal Society of Canada

Among the speakers at the Clinical Congress conducted by the Connecticut State Medical Society in New Haven, September 29-October 1, were

- Dr William W Herrick, F A C P, New York, N Y—"Medical Aspects of Obstetrics",
 Dr Lester M Morrison, F A C P, Philadelphia, Pa—"Chemotherapy of the Gastro-intestinal Tract",
 Dr Maxwell Finland, F A C P, Boston, Mass—"Chemotherapy in the Bacteremias";
 Dr Francis G Blake, F A C P, New Haven Conn—"Use of Penicillin"

Dr Harrison F Flippin, F A C P , Philadelphia, Pa , and Dr Harry F Dowling (Associate), Washington, D C , participated in a panel discussion on "The Sulfonamides" at the 14th Annual Scientific Assembly of the Medical Society of the District of Columbia, September 29-October 1

Dr William F Kendall, F A C P , has been appointed Manager at the Veterans Administration Facility, Dwight, Ill

Dr Lay Martin, F A C P , Baltimore, Md , is making a trip through Central and South America under an appointment by Nelson A Rockefeller, Coordinator of Inter-American Affairs

Dr Henry A Christian, F A C P , Brookline, Mass , Hersey Professor of the Theory and Practice of Physic, Emeritus, has been invited to return to active duty to give clinical instruction, by the President and Fellows of Harvard University. Dr Christian has also been appointed Visiting Physician at the Beth Israel Hospital, Boston

Dr Ivor E Reed, F A C P , Detroit, has been appointed a member of a technical advisory committee to the Michigan Crippled Children Commission

Dr Robert A Peers, F A C P , Colfax, Calif , spoke on "Control of Tuberculosis in the Individual Patient and Among His Contacts" at a meeting of the Nevada State Medical Association in Reno, September 24-26

Dr Charles H Marcy, F A C P , Pittsburgh, spoke on "Tuberculosis and the Home Front" and Dr Herbert T Kelly, F A C P , Philadelphia, Pa , spoke on "Nutrition and the War Effort" at the 3rd Pennsylvania Health Institute, held in Harrisburg, September 28-30

Dr Herbert Z Giffin, F A C P , Rochester, spoke on "Miscellaneous Observations on the Diagnosis and Treatment of Anemia" and Dr Walter S Neff (Associate), Virginia, spoke on "Shock Associated with Burns" at the annual session of the Northern Minnesota Medical Association in Bemidji, August 29

Under the Presidency of Dr Jess V Bell, F A C P , Kansas City, Mo , the Kansas City Southwest Clinical Society held its annual fall conference, October 5-8, 1942. Among the guest speakers were

Dr Cornelius P Rhoads, F A C P , New York, N Y—"Nutrition and Cancer",
Dr Byrl R Kirklin, F A C P , Rochester, Minn—"Cancer of the Gastrointestinal Tract Its Early Manifestations",

- Dr S Marx White, F A C P, Minneapolis, Minn—"Management and Training for the Patient with Essential Hypertension",
 Dr Wesley W Spink, F A C P, Minneapolis, Minn—"Chemotherapy of Infectious Diseases",
 Dr Richard H Freyberg (Associate), Ann Arbor, Mich—"General Management of the Patient with Rheumatoid Arthritis"
-

Dr Chester S Keefer, F A C P, Boston, Mass, spoke on "Some of the Problems Concerned with the Interpretation of Abdominal Pain" at the annual meeting of the Vermont State Medical Society in Montpelier, October 1

The Medical Society of Virginia held its annual meeting in Roanoke, October 5-7. The guest speakers at this meeting were Dr James E Paullin, F A C P, Atlanta, Ga, President of the College, and Dr Julian M Ruffin, F A C P, Durham, N C. Among the Virginia physicians who participated were

- Dr T Dewey Davis, F A C P, Richmond—"Acute Cirrhosis of the Liver",
 Dr Paul D Camp, F A C P, Richmond—"Rheumatic Fever and Rheumatic Heart Disease in Virginia",
 Dr David C Wilson, F A C P, Charlottesville—"Treatment of the Mental Diseases Related to the Involutional Period"
-

Under the Presidency of Dr George R Minot, F A C P, Boston, Mass, the 27th Annual International Medical Assembly of the Inter-State Postgraduate Medical Association of North America was held in Chicago, Ill, October 26-30. Among the members of the College who spoke were

- Dr Elmer L Sevringhaus, F A C P, Madison, Wis—"The Male Climacteric",
 Dr Tom D Spies, F A C P, Cincinnati, Ohio—"The Use and Abuse of Vitamins"
-

Dr Louis H Clerf, F A C P, Philadelphia, Pa, spoke on "Cricopharyngeal Spasm" and Dr John A Kolmer, F A C P, Philadelphia, Pa, participated in a symposium on "Chemotherapy" at the 47th Annual Meeting of the American Academy of Ophthalmology and Otolaryngology, held in Chicago, Ill, October 11-14, 1942

The Joint Committee on Post-Graduate Education of the Long Island College of Medicine and the Medical Society of the County of Kings conducted postgraduate courses in the various branches of medicine, including arthritis, clinical cardiology, gastro-enterology, hematology, and diabetes. The courses began early in October.

Dr Simon R Blatteis, F A C P, Brooklyn, is Chairman of the Joint Committee, and Dr Jean A Curran, F A C P, is the representative of the Long Island College of Medicine.

1942 SUPPLEMENT TO THE A C P DIRECTORY PUBLISHED

As of September 1, 1942, a Supplement to the 1941 Directory of the American College of Physicians was published and distributed to all members in good standing, with the exception of members on active military duty in the field. It was felt that this Supplement would be of no immediate value to these men on active duty, but the Executive Offices of the College will gladly mail a copy on request and without charge to any of these members.

The Supplement contains the names of Officers, Regents and Governors for the current year, committee personnel, new regulations, additions to Life Membership, records of awards of the Phillips Medal and of research fellowships, advancements to Fellowship during the past year and additions to the geographical and alphabetical rosters of members. In addition it has a record of members reported missing in military action, a list of deceased members and a list of those who have been removed from the roster by resignation or for other reasons.

PORTRAITS OF EARLY MEDICAL HEROES PRESENTED TO SURGEONS GENERAL
OF ARMY AND NAVY

Portraits of six early Surgeons General of the Army and Navy have recently been presented to the respective medical services of the Army and Navy by Ciba Pharmaceutical Products, Inc., of Summit, N. J. The paintings were by Ishmael, and the studies of these men who helped to found the medical services were reconstructed from all available early sketches and prints, in which the artist was aided by Col. Harold W. Jones, F. A. C. P., Librarian, Army Medical Library, and Capt. Louis H. Roddis, F. A. C. P., Editor of the Naval Medical Bulletin. Backgrounds of the paintings were suggestive of the exploits of the subjects, who were:

William Paul Crillon Barton, the first Chief of the Bureau of Medicine and Surgery of the Navy, 1786-1856

Jonathan M. Foltz, Chief of the Bureau of Medicine and Surgery and Surgeon General, U. S. Navy, 1810-1877

Elisha Kent Kane, Medical Officer of the U. S. Navy, 1820-1857

Charles S. Tripler, Brigadier General, Army Medical Corps, 1806-1866

Jonathan Letterman, Surgeon Major, U. S. Army, 1824-1872

Bernard J. D. Irwin, Brigadier General, Army Medical Corps, 1830-1917

Together, these men form a body of scientific pioneers who helped to establish the medical services of the Army and Navy and make them the great implement for the saving of life they are today. Barton standardized medical supplies, made of the crude sick bay a hospital and was responsible for placing a medical library in each unit. Foltz, known as Surgeon of the Seas because of his wide service, saw the transition of wooden ships to iron ones and forwarded in many ways the Navy in hygiene. Kane headed an expedition into the Arctic to seek a missing brother officer and during that trip added much to our knowledge of the treatment of scurvy. Tripler, of the Army, standardized the selection of recruits and wrote a manual which is still the basis of our standardization of the new Army men. Letterman established the first Ambulance Corps which was tested during the bloody Battle of Fredericksburg, and became standard practice in the Union Army. Letterman General Hospital in San Francisco is named in his honor. Irwin, during the Battle of Shiloh organized the first tent hospital which has served as a model for field hospitals ever since. The site of his original hospital is marked with a Government tablet.

The presentation of the portraits of the Navy heroes was made to Rear Admiral Charles M. Oman, M.D., U. S. Navy, at the new National Naval Medical Center at Bethesda, Md., where the portraits will be hung in the library for present and future generations of the Navy physicians to see.

The presentation of the portraits of the Army Surgeons General was made in the stately old Army Medical Library. Colonel Harold W. Jones, F.A.C.P., Medical Corps, U. S. Army, accepted them from Mr. Brodbeck on behalf of the Surgeon General of the Army. The Army Medical Library contains many handsome portraits of past officers of the Army Medical Service and these three will be added to the collection.

PAY-YOUR-DOCTOR-WEEK

The Fifth Annual Pay-Your-Doctor-Week was observed November 1-7, in Los Angeles and several other cities. The plan, inaugurated in 1938 by the California Bank of Los Angeles, suggests to the public that they should not only pay their doctors, but also arrange to retire all outstanding debts and place themselves upon a cash basis, thus supporting the contention of the administration that to get out of debt is a patriotic duty—in fact, a necessity in order that the public may meet the increasing tax load and their responsibilities to buy more War Bonds.

The American Public Health Association held its 71st Annual Meeting in St. Louis, October 27-30. Some twenty other organizations in the public health field held meetings and conferences at the same time. The program was largely devoted to war time health problems—nutrition, industrial hygiene, the control of communicable diseases, maternal and child health and housing.

The U. S. Census Bureau has inaugurated a health program providing extensive medical facilities for its employees in its new building at Surtland, Md. Dr. Leon Schwartz (Associate), formerly of Philadelphia, but now in the U. S. Public Health Service, has been placed in charge. He will be assisted by a supervising nurse and a group of junior nurses. Necessary examining equipment, including mobile x-ray units, has been installed. The census unit will make preplacement physical examinations, supplementing those required for employment by the Civil Service Commission, and will treat illnesses or injuries of employees that develop during their time at work. However, actual treatment will be left to family physicians. Health records will be kept for each worker and studies will be carried on to prevent or reduce loss of time due to occupational and other diseases.

WAR PRODUCTION BOARD SEEKS USED STANDARD TYPEWRITERS FROM GENERAL PUBLIC

The War Production Board announces a need for 500,000 standard typewriters made after January 1, 1935, for use in the Army, Navy and Government departments. Purchases based on trade-in allowance value as of February 1, 1941, will be made through typewriter manufacturers' representatives and approved dealers, who will condition the typewriter and ship it direct to the nearest Army or Navy supply depot. At the time the seller delivers his typewriter, the buying agent will issue a Procure-

ment Division Receipt and will place a decalcomania label on the typewriter, reading, "Property of the U S Government"

Manufacturers' records indicate the quantity and ownership of the majority of typewriters in civilian hands, which are suitable for military needs, and this appeal is made to present a fair opportunity to owners of such equipment to voluntarily assist in raising the required number of machines for sale to the Government "A prompt response to this appeal will forestall and be preferable to any requisitioning of typing equipment on Government order, and your patriotic intentions will be measured by the cooperation and effort made to obtain the machines needed"

The American Gastroenterological Association on January 1, 1943, will publish the first issue of a new Journal to be called, GASTROENTEROLOGY The new Journal will be owned by the Association, will be the official publication of the Association, and will be published by Williams and Wilkins Company It will appear monthly, and the subscription price will be \$6 00 per year

Dr W C Alvarez will be the Editor (after June, 1943) and Dr A C Ivy will be the Assistant Editor The Editorial Board will consist of Drs A H Aaron (Buffalo), J A Barger (Rochester), H L Bockus (Philadelphia), W C Boeck (Los Angeles), B B Crohn (New York), R Elman (St Louis), F Hollander (New York), Sara Jordan (Boston), J L Kantor (New York), B R Kirklin (Rochester), P Klemperer (New York), F H Lahey (Boston), F C Mann (Rochester), H J Moersch (Rochester), V C Myers (Cleveland), W L Palmer (Chicago), J M Ruffin (Durham), R Schindler (Chicago), and D L Wilbur (San Francisco)

Gastroenterology invites for publication clinical and investigative contributions which are of interest to the general practitioner as well as to the specialist and which deal with the diseases of digestion and nutrition, including their physiological, biochemical, pathological, parasitological, radiological and surgical aspects

Manuscripts should be sent to Dr A C Ivy, *Gastroenterology*, 303 East Chicago Avenue, Chicago, Illinois Letters regarding subscriptions and business matters should be addressed to Mr R S Gill, Williams and Wilkins Company, Baltimore, Maryland

OBITUARY

DR WILLIAM DICK CUTTER

William Dick Cutter, Chicago, aged 63, Fellow of the American College of Physicians since 1929 and Secretary of the Council on Medical Education and Hospitals of the American Medical Association since 1931, died of coronary thrombosis at the home of his daughter in Johnson City, Tennessee, January 22, 1942

Dr Cutter was born in Brooklyn, New York, September 14, 1878. He attended Adelphi Academy of Brooklyn, received an A B degree in 1899 from Yale University, and an M D degree from Johns Hopkins in 1905. After graduation from Yale he served as Assistant in Biochemistry at Columbia University for two years during which time he also did graduate work in Berne, Switzerland. He served an internship in the French Hospital in New York City, and then spent five years on the hospital staff of the Copper Queen Consolidated Mining Company in Bisbee, Arizona. From 1911 to 1919 he was Professor of Pharmacology and Physiology at the University of Georgia Medical School. It was during this time that he became interested in medical education and improved standards of medical practice. He served as Secretary of the Board of Medical Examiners, New York State Board of Regents, from 1919 to 1923, then as Dean of the New York Postgraduate Medical School for five years, and for the next three years as Dean of the School of Medicine of the University of Southern California.

In 1931 he was appointed Secretary of the Council on Medical Education and Hospitals of the American Medical Association, a position to which he gave all his skill, energy and devotion for the remainder of his life. His careful compilation and study of the facts concerning various problems were essential before he expressed an opinion or reached a conclusion. He kept abreast of medical education and the problems peculiar to each medical school. Even when he was obliged to make an unfavorable ruling, the recipient felt that Dr Cutter was fair and sympathetic. Dr Cutter's forte was the preparation of the large and small details of numerous problems for later review by the Council.

He was a member of Phi Beta Kappa, Sigma Xi, the Association for the Advancement of Science, the Institute of Medicine of Chicago, the American Medical Association and the American College of Physicians. Since 1933 he served as Manager-editor of the Federation Bulletin of the State Medical Boards.

Dr Cutter was a warrior ever ready to defend a principle, firm—a bit stubborn at times, honest, conservative, with faith in the slow evolution of the human race and the human individual, with a fine, mild character which at all times upheld the high position of the medical profession. We last saw him officially at the April round-up of our regional conference, happy, alert, witty, and in the company of medical men "whom he liked."

LEROY H. SLOAN, M D, F A C P,
Governor for Northern Illinois

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MODERN VIEWS ON THE TREATMENT AND PREVENTION OF HOOKWORM DISEASE*

By JUSTIN ANDREWS, Sc D, *Atlanta, Georgia*

Hookworms were first observed in man 104 years ago¹, they were known to have become well-naturalized citizens of this hemisphere some 60 years later². Although their etiological rôle was taken for granted prior to that time, most of our reasonably exact information concerning their life-history, transmission, distribution, social and economic significance and control has accumulated since the turn of the century. Many of these facts, familiar to parasitologists, have not yet found their way into medical texts. They appear intermittently in current medical journals in abbreviated form usually without interpretation. The object of this paper, therefore, is to present a synoptic review, momentarily up-to-date, of information about one of these items—namely, control—from the standpoint both of the private practitioner concerned with the cure of the sickness caused by hookworms and of the public health official whose basic aim is the prevention of hookworm disease.

Shortly after hookworms were recognized as being a cause of disease in man,^{3,4} their removal was attempted by means of drugs known to have anthelmintic values against other worms such as tapeworms and large roundworms. These included male-fern, cusso, kamala, santonin, turpentine, benzene, etc., but none of these was uniformly satisfactory, the best of the lot being the ethereal extract of male-fern⁴. This was rapidly replaced by thymol⁵ which remained the standard anti-hookworm remedy for over 30 years, although beta-naphthol⁶ was popular in some parts of the world, especially the Orient. In 1913, chenopodium, long known to have potent anthelmintic and some other less desirable properties, was reported on favorably⁷ for its activity against hookworms and *Ascaris*. During the

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next decade, it was the drug of choice in expelling hookworms and is still used extensively for this purpose

That brings us up to comparatively recent times. In 1921 a veterinary parasitologist, Maurice C. Hall,⁸ working with compounds of carbon and chlorine, found that carbon tetrachloride was amazingly efficient in removing hookworms from dogs. Toxicity tests on dogs, monkeys and finally man seemed to justify its administration to cases of human hookworm disease and well over a million individuals have been treated with this drug.

It is undoubtedly the most effective and most conveniently administered hookworm anthelmintic now known. It is commonly employed in 3 or 4 c c doses for adults in water, milk or capsules either with or followed by saline purgation. It acts directly on the worms as it passes through the intestines, removing from 95 to 99 per cent of the type found in this country and completely defaunating from 60 to 90 per cent of the cases with a single treatment.

Carbon tetrachloride is not without its hazards, however. In the first place, it is occasionally, though rarely, toxic. The number of instances of severe poisoning and of death associated with its use is extremely small and might reasonably be charged to chance were it not for the fact that the majority of them manifest a uniformity of syndrome which is experimentally reproducible in lower animals by administration of the drug. This includes irritation of the gastrointestinal tract, excitability followed by depression, bilirubinemia, retention of guanidine in the blood, hypoglycemia and unconsciousness, sometimes with convulsions, not infrequently leading to death.

It has been clearly demonstrated that these effects are not generally due to overdoses of the drug nor to impurities contained in it. These unfortunate developments are difficult, if not impossible, to anticipate and occur without significant frequency in all groups except alcoholics. Lambert⁹ treated 50,000 cases in Fiji without serious consequences and then had two deaths in a single week.

The chain of circumstances in these cases seems to be as follows: carbon tetrachloride, like its chemical sibling, chloroform, is an anesthetic with a strong predilection for hepatic tissues. The liver rapidly absorbs the drug from the blood and detoxicates it but, in some instances at least, is gravely injured by the process. This acute necrosis interferes with normal hepatic glycogenolysis and increases the amount of bile pigments in the blood. These combine with the blood calcium reducing the reserve calcium in the tissues and increasing its elimination from the body. The loss of ionized calcium in the blood may be one factor in the intoxication syndrome, but what seems to be of even greater importance is the abnormal accumulation of guanidine in the circulation. The elaboration of this noxious substance in unusual amounts is also due, presumably, to liver injury. Calcium has an antagonistic and highly beneficial effect in guanidine poisoning. The depletion of calcium, occasioned by the bilirubinemia permits high blood concentrations of guanidine with consequent toxic manifestations.

These demonstrations^{10, 11} have led to important practices in the prevention or cure of carbon tetrachloride poisoning, namely the prophylactic or therapeutic use of diets rich in carbohydrates and calcium and poor in fats and meats and, under emergency conditions, the parenteral administration of calcium and sugar

Two other circumstances may lead to complications in the use of this drug. The first of these is the consumption of alcohol either prior to or during treatment. The cirrhotic liver of chronic alcoholics is in no condition to withstand the unusual strain placed upon it by this preparation. Thus, it fails more rapidly and more frequently than does the normal liver, resulting in the succession of circumstances mentioned above. Alcohol taken *with* carbon tetrachloride frequently results in violent and continuous nausea and vomiting, sometimes with intestinal hemorrhage, jaundice, delirium, convulsions and death. Thus carbon tetrachloride should not be given to persons known to be habitually addicted to the use of alcohol and this stimulant should be strictly forbidden during treatment.

Heavy roundworm infections may also be a source of danger. This drug stimulates these large parasites to abnormal activity, resulting in the formation of solid plugs of their bodies obstructing the intestine or in their migration anteriorly into the common bile or pancreatic ducts or the pharynx whence they may be extruded through the mouth or nose. It is, therefore, of paramount importance (1) to ascertain by adequate laboratory examination whether or not ascarids as well as hookworms are present, and (2) if they are, to see to their removal before proceeding with carbon tetrachloride treatment. This may be readily accomplished with either chenopodium or hexylresorcinol.

In an effort to increase the antihookworm efficiency of carbon tetrachloride, to minimize its dangers when roundworms are present, and generally to facilitate anthelmintic treatment under such conditions, various mixtures of carbon tetrachloride and oil of chenopodium⁹ or ascaridol,¹² its active principle, were introduced and have been very popular. These are highly effective combinations for the expulsion of both hookworms and roundworms but, it must be remembered, contain elements of danger from two sources rather than only one. These properties are not supplemental as the injuries caused by carbon tetrachloride are mainly hepatic, whereas those due to chenopodium are directed against the central nervous system. Such compound anthelmintics should be administered only under the careful supervision of a watchful physician.

Hall¹³ likewise directed attention to the hookworm-removing attributes of tetrachlorethylene. It is closely related chemically to carbon tetrachloride and is used in the same dosage. Although it is not as effective as the other drug, it seems to be almost entirely devoid of its toxic propensities due to its lower solubility in aqueous systems and to its minimal absorption from the intestine. Its efficiency varies in the hands of different investigators. Our own observations on carefully controlled cases convince us that

although a single treatment will not get rid of the last hookworm from more than 50 per cent of our patients, it will remove about 90 per cent of all hookworms. Two treatments with tetrachlorethylene are about equivalent to and are much safer than a single dose of carbon tetrachloride in dislodging hookworms. In spite of its lower efficiency, it is preferred by most helminthologists because of its greater safety. There are virtually no contraindications to its use except alcoholism and ascariasis. A mixture of tetrachlorethylene and oil of chenopodium used under this last circumstance has received favorable report¹⁴

The latest anthelmintic of significant merit is hexylresorcinol introduced as an ascaricide in 1930¹⁵. It is mentioned here because of its incidental hookworm-removal value. In 1 gm doses for adults it removes practically all roundworms and about 70 per cent of the hookworms, though only a comparatively small percentage of patients are rendered hookworm-free from a single dose. If the pills are swallowed (not chewed), there are no known contraindications and it can be given repeatedly even to small children, aged persons and debilitated individuals. It is, therefore, an ideal drug for prehookworm treatment when *Ascaris* is present.

Briefly summarizing these current contributions to our knowledge of the treatment of hookworm disease, we may conclude that, from the standpoints of safety and efficiency, tetrachlorethylene is the best drug for use in uncomplicated hookworm infection. When roundworms are also present, hexylresorcinol followed by tetrachlorethylene or several hexylresorcinol treatments in rapid succession will give most satisfactory results. Carbon tetrachloride and oil of chenopodium are potent but unsafe anthelmintics, the older vermifuges lack both safety and efficiency.

In the public-health field of hookworm-disease prevention, similar shifts in principle and procedure have evolved. The activities of the Rockefeller Sanitary Commission from 1910 to 1914 had numerous and far-reaching effects. That their mass treatments served to reduce the incidence and, presumably, the intensity of hookworm infection in the southern states seems clearly indicated by the studies of Keller, Leathers and their associates¹⁶. The educational efforts which supplemented the treatment campaign generated interest in and a desire for local health facilities especially among rural populations. Perhaps the greatest consequence was the stimulation of scientific interest in the subject of hookworm disease and its control. Laboratory and field researches were carried on the world over.

Space and time limitations forbid the summarizing of the information gained as a result of these endeavors. It is interesting to note, however, that this study, like most intensive and extensive inquiries, progressed rapidly from the stage of qualitative exploration to that of quantitative analysis. This led to a concept of hookworm disease with which most medical men and many public health officials do not seem to be familiar.

Briefly expressed, it attempts to distinguish between *hookworm disease* in its most literal sense and *subclinical hookworm infection*, which is gen-

erally much more common. The distinction is based on the number of worms present and the nutritional status of the host as shown in the following argument with its implications concerning hookworm-disease control.

- 1 Adult hookworms suck blood continuously. The amount removed is *proportional to the number of hookworms present*.
- 2 If they remove blood more rapidly than it can be formed *HOOKWORM DISEASE (anemia) results, if not*, the condition is one of *subclinical hookworm infection*.
- 3 The primary objective of public health authorities should be the *detection, prevention and control of HOOKWORM DISEASE* rather than the elimination of subclinical hookworm infection.
- 4 Inasmuch as the rate of blood removal by hookworms varies directly with the number present and the rate of hemoglobin formation is normally governed by iron and protein intake, it follows that
 - a Hookworm disease is more likely to occur and will be more severe when worm burdens are high and iron-protein consumption low.
 - b When adequate iron-protein consumption prevails, hookworm infection, with rare exceptions, will be subclinical whether worm burdens are heavy or light.
 - c When diets are iron-protein deficient, a chronic, progressive anemia will develop irrespective of the presence or absence of hookworms.
- 5 Therefore, even in hookworm-infested areas, all instances of anemia are not necessarily cases of hookworm disease. *Intelligently planned hookworm-disease control must distinguish between anemias caused or augmented by hookworms and those due to other causes*.
- 6 To accomplish the control of hookworm disease, knowledge of the *intensity* as well as the *incidence* of hookworm infection must be considered in relation to the *non-hookworm anemias* of the people concerned.

In considering this reasoning, it must be remembered that hookworm, like many other helminthic infections, is fundamentally different from bacterial or protozoan infections in that the causative organism—hookworms—does *not* multiply within the body of its host. Indeed, there is good evidence to show¹⁷ that if the entrance of hookworm larvae to the body is prevented, the number of hookworms remaining not only fails to increase but actually diminishes at a relatively rapid rate. This, of course, is the basis for public health reliance upon sanitary excreta-disposal facilities for homes and schools in the control of hookworm disease.

Thus, emphasis is shifting from hookworm infection to hookworm disease. We no longer advocate the random examination of school children, but rather the selective survey of anemic persons in school or out, under 20

years of age. This amounts to an investigation of "suspects." Stool specimens are examined in the laboratory first of all by brine flotation to identify all egg-positive individuals. Their stools are then subjected to an egg-counting procedure which indicates the approximate number of hookworm eggs per unit of stool. Inasmuch as the number of worms present varies directly with the magnitude of the egg-count, this gives a rough measure of the intensity of the infection, permitting the separation of persons with a sufficiently heavy worm-burden to cause anemia from those whose worm burdens are so light that the observed anemia is probably due to some

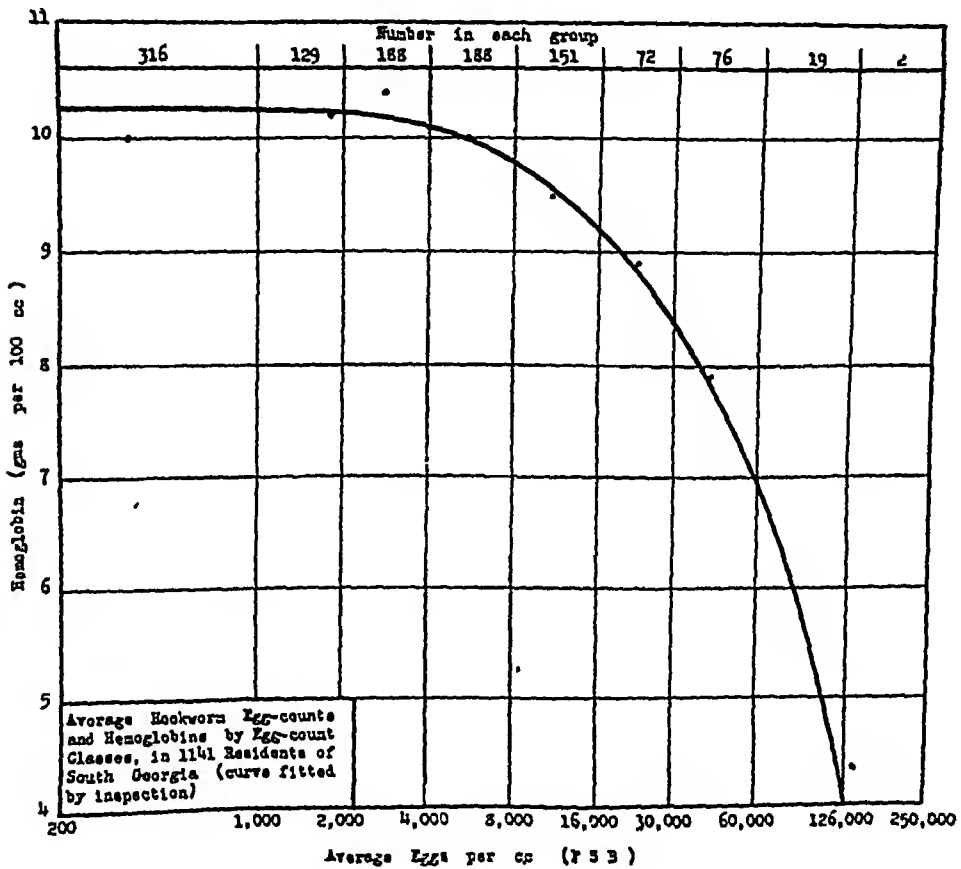


FIG 1

cause other than hookworms. Here in Georgia we have set 5,000 eggs per cc, an egg-concentration which is roughly equivalent to 200 worms, as the level above which we will do hookworm-control follow-up, below which we ignore the presence of hookworms and start looking for some other cause of anemia. Our basis for this particular figure is shown in the accompanying curve (figure 1) in which it is apparent that not much change in hemoglobin levels is associated with hookworm infection until worm burdens equivalent to 5,000 eggs per cc are reached.

Modern hookworm investigation-and-control technic centers on the family instead of the individual. The probability of high rates of family incidence is obvious when one considers that the infection is transmitted

primarily through bare feet in contact with polluted soil. This combination of circumstances occurs most frequently in the environs of the home and is more likely to occur around certain homes than around others. Thus, the

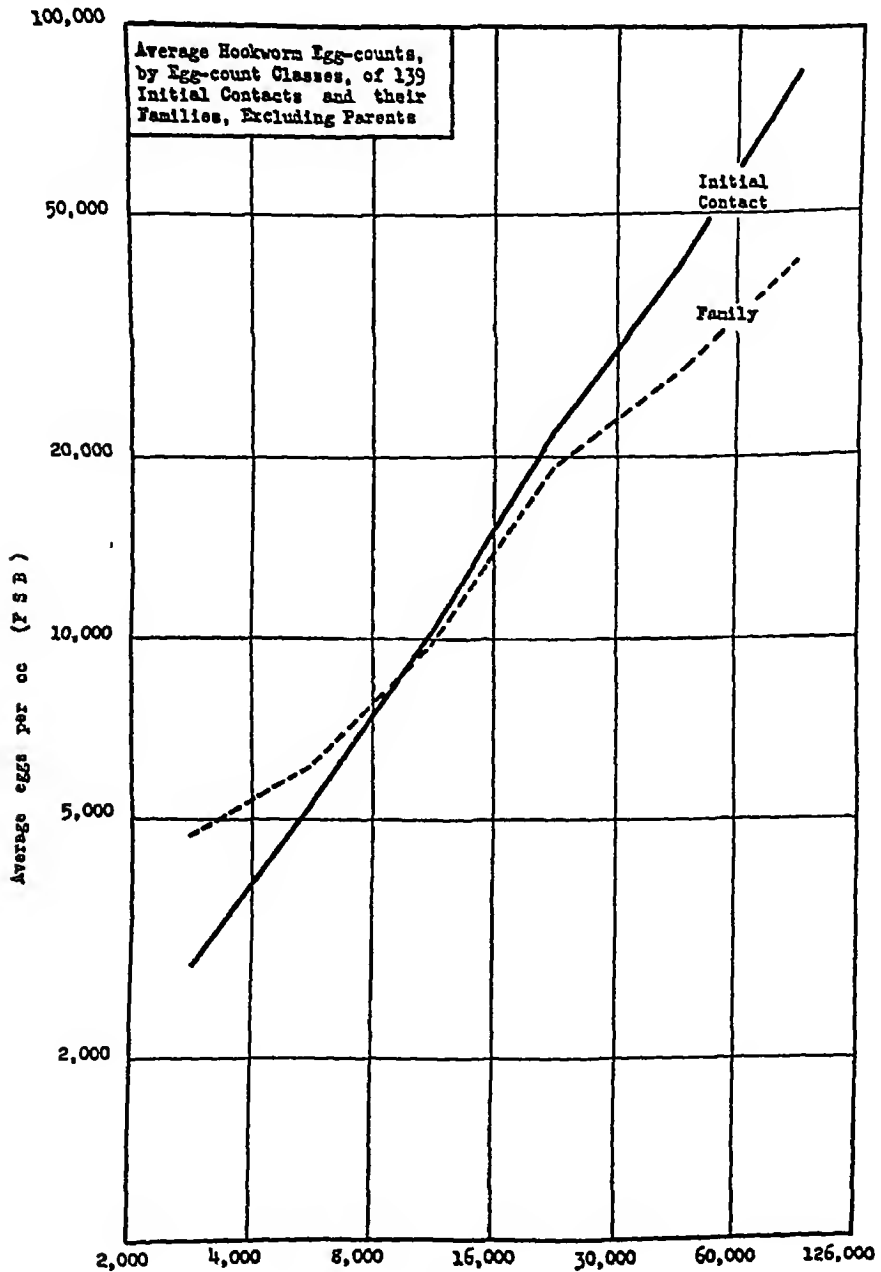


FIG 2

intensity as well as the incidence of infection revolves around the family. This is indicated in the accompanying figure (figure 2) in which the solid line represents the locus of average egg-counts, by egg-count classes, of "initial contacts," that is, the first anemic member of the family seen, under

20 years of age, while the broken line shows the same information for the 139 families of which they are members. It will be observed that the average egg-counts of the families increase with those of the "initial contacts", thus, the intensity of infection in the initial contact turns out to be fairly representative of the average family worm burden. This means that families needing hookworm relief can be identified from these initial contacts and that, as a general rule, it is unnecessary to examine other members of the suspected families if, for example, group treatment is planned as the control measure.

What is to be done for these hookworm-disease families once they are identified? First of all, their sick members must be made well. This requires medical service, and as far as possible, is handled by private physicians in Georgia. Indigency is high, however, among hookworm sufferers, and it is usually the expressed desire of local medical groups or practitioners that health doctors assume treatment responsibilities for such patients. Anthelmintic drugs are supplied gratis to medical men by the State.

The therapeutic problem is a dual one consisting of worm removal and treatment of the anemia. As Payne and Payne¹⁹ and others^{18, 20} have recently shown, hemoglobin recovery following worm expulsion without iron therapy is a long-drawn-out process. This is especially true when dietaries are iron deficient. On the other hand although iron administration alone produces rapid improvement in the blood picture, the gains are not sustained unless the worms are removed^{19, 20}. In Georgia we do both, giving iron, usually as Bland's pills, *before* deworming if the anemia is exceptionally severe, i.e., hemoglobin level of 5 gm or less, *after* worm removal if the anemia is moderate. Educational efforts are made thereafter, to improve the dietary so that greater iron intake in food is provided especially for growing children in whom the concurrence of hookworm anemia and nutritional anemia is most marked.

The prevention of hookworm disease is, first of all, a matter of sanitation, i.e., the provision of approved excreta-disposal facilities, secondly, education concerning their use and the physical benefits that will result therefrom. The sale and use of sanitary sewage-disposal structures for homes and schools is, therefore, vigorously promoted but in these days of progressively restricted WPA participation in community sanitation projects, of increasing costs and decreasing availability of materials and of labor, the prospects of preventing any great amount of hookworm transmission by the use of standard sanitary units are comparatively remote. Families that cannot afford minimal medical service cannot afford pit privies.

In those numerous instances, therefore, in which home sanitation cannot be provided, an attempt is being made in this State to develop more definitely preventive values from anthelmintic treatment than it provides as ordinarily administered.

As indicated above, individuals suffering from hookworm anemia are treated with iron and tetrachlorethylene as fast as they are discovered ir-

respective of whether or not the premises are to be sanitized. The deworming of other members of the family at that time is not encouraged. If a pit privy is provided and used, there will be no increase in the intensity of infection and so family treatment is not necessary. If, however, the household must get along without sanitary facilities, at least one and desirably two worm-removal treatments are urged for *all* members of the family during the cold winter months of the year. The object here is to reduce and, if possible, to eliminate the family worm burden at a time when immediate reinfection is less likely than during the summer months. The unfavorable effect on non-parasitic stages of hookworms of temperatures below 50° F has been noted by various observers. Augustine,²¹ working in southern Alabama, was unable to find larvae in polluted soil from the latter part of December into March. Our own findings in south Georgia, incomplete and inconclusive, confirm this observation. Thus it appears that the soil in this area tends to become free from infective larvae during the winter months and the likelihood of reinfection following treatment at this season is correspondingly remote. This seasonal prophylactic effect is enhanced by the fact that it is during the cold months of the year that rural residents wear shoes if they ever wear them at all.

A last anti-hookworm possibility, at present in its incipient stage, may in the long run surpass in importance either sanitation or treatment. The experiments of Cort and Otto²² and their students^{23, 24, 25} on hookworm disease in dogs suggest (1) that a highly protective, specific immunity to hookworms and hookworm disease may be developed by experience with the infection, and (2) that this resistance can be broken and rendered ineffective by dietary deficiency. This effect is entirely separate and distinct from the inability to exert hematopoietic potentialities to their utmost because of inadequate iron-and-protein consumption. Its most striking demonstration is in the case of previously immunized dogs whose resistance, reduced by deficient diet, is suddenly restored by adequate dietary supplements. Under these conditions, the dogs recover clinically, lose worms spontaneously and resist further infection.

It would be entirely premature to assume from the above that the man-hookworm system will interact as the dog-hookworm system has been shown to do. Nevertheless, there is abundant epidemiologic evidence to suggest that this relationship may prevail and, as far as I know, none to refute it. Perhaps the time may come, therefore, when we will know that we can prevent and cure human hookworm disease by dietary manipulation, income and gustatory fancy permitting.

In summarizing the preventive aspects of this subject, it may be said that although sanitation, treatment and education remain the familiar armamentarium of the hookworm fighter, then application is now ordered and refined as never before (1) by discrimination between hookworm disease and subclinical hookworm infection, (2) by differentiating between the anemia due to hookworms and those due to other causes, and (3) by the

recognition of the family rather than the individual as the unit of investigation and control. The relation of diet to hookworm infection and its prevention is already known to be important, present knowledge suggests that it may become more so in the future.

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MYELOID HYPERPLASIA AND METAPLASIA INDUCED BY EXTRACTS OF URINE FROM PATIENTS WITH MYELOGENOUS LEUKEMIA *

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IN previous brief reports,^{1, 2} the effect in guinea pigs of injection of extracts of urine from patients with leukemia has been described. The results indicated that extracts of urine from patients with chronic myeloid leukemia produced myeloid hyperplasia and metaplasia in the organs of guinea pigs with considerably greater frequency than did extracts of urine from patients with other diseases and from normal people.

Four different methods of extraction were effective in recovering the active material from the urine of patients with chronic myeloid leukemia. These included the original kaolin adsorption, a benzoic acid adsorption, and a chloroform extraction. The product of the latter was divided into two fractions, both of which had some activity. All of these methods have been adapted from standard procedures used to recover certain of the endocrine products from urine.

EXPERIMENTAL

Urine was obtained from patients with chronic myeloid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, acute lymphoid leukemia, acute monocytic leukemia (Schilling type), Hodgkin's disease, multiple myeloma, aplastic anemia, infectious mononucleosis, and carcinomatosis. Sufficient urine could not be obtained from each type of disease to make extracts by each of the methods, and the major part of the investigation was done with extracts of urine from patients with chronic myeloid leukemia, chronic lymphoid leukemia, and from normal individuals.

Guinea pigs were employed as experimental animals. These were young, male animals weighing between 180 and 250 grams at the beginning of the experiment. No attempt was made to secure a uniform strain. The guinea pig was selected because it is a convenient size and because spontaneous leukemia seldom occurs in this animal. Mice, rats, rabbits, and monkeys were used in small numbers but because of difficulties encountered, further experimentation with them has been postponed.

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Guinea pigs received the extracts of urine in daily subcutaneous injections varying in volume from 0.1 to 10 c.c. and representing from 60 c.c. to 800 c.c. of original urine. Details of dosage will be amplified as each extract is described. The injections were continued for a period generally not exceeding 10 weeks, if death had not occurred sooner. Most of the animals died or were sacrificed within that period of time.

Complete autopsy was performed as soon after death as possible. The wet weight of the spleen and liver were recorded routinely. Sections were obtained from femoral, tibial, and humeral marrows, spleen, liver, lymph nodes, kidney, adrenal, heart, and lungs. Impression films were made of marrow, spleen, and liver and stained with Wright's stain. Slices of the organs were placed in acid-Zenker's solution, and the sections made from these were stained with hematoxylin and eosin. Special stains on fixed tissue sections, including Wright, Mallory, Maximow, and Giemsa stains were made in several instances. The peripheral blood of the animals was examined not less than once a week during the course of the injections. This examination included a hemoglobin estimation (Sahli method), white blood count, and differential blood count.

RESULTS

Approximately half the animals receiving extracts of urine from patients with chronic myeloid leukemia showed evidence of myeloid hyperplasia and metaplasia. Only about 15 per cent of animals receiving extracts of urine from individuals not having myeloid leukemia showed a similar response, and in these animals, the response was generally less marked.

Many of the animals which subsequently showed the myeloid response became ill, and either failed to gain or actually lost weight. The changes in the blood of these animals were not constant. In a great many animals, nothing more than a mild anemia was noted. In some, a severe hypochromic anemia, with hemoglobin as low as 45 per cent (70 grams) developed. Nucleated red cells and polychromatophilia were present. A few of these animals had free blood in the peritoneal cavity at autopsy, the exact origin of which could not be determined.

The white blood counts ranged from normal to moderately elevated, few being in excess of 25,000. The majority of cells were adult polymorphonuclear neutrophils. In animals with elevated white blood counts, a small number of myelocytes and blast cells were present. The blood platelets were not altered. We do not feel that the changes in the peripheral blood were specific. They probably only reflected the general condition of the animal.

There was little gross change in the organs at autopsy. In some animals, the spleen was considerably enlarged, weighing as much as 40 grams. Some of the smallest spleens (0.25 gram wet weight), however,

showed the most marked histological changes. On cutting the spleens, the follicular structure was found to be obliterated or less prominent than normal. The bone marrow generally appeared grossly normal, although in a few instances it was redder and less fatty than normal. Other organs did not show any gross changes.

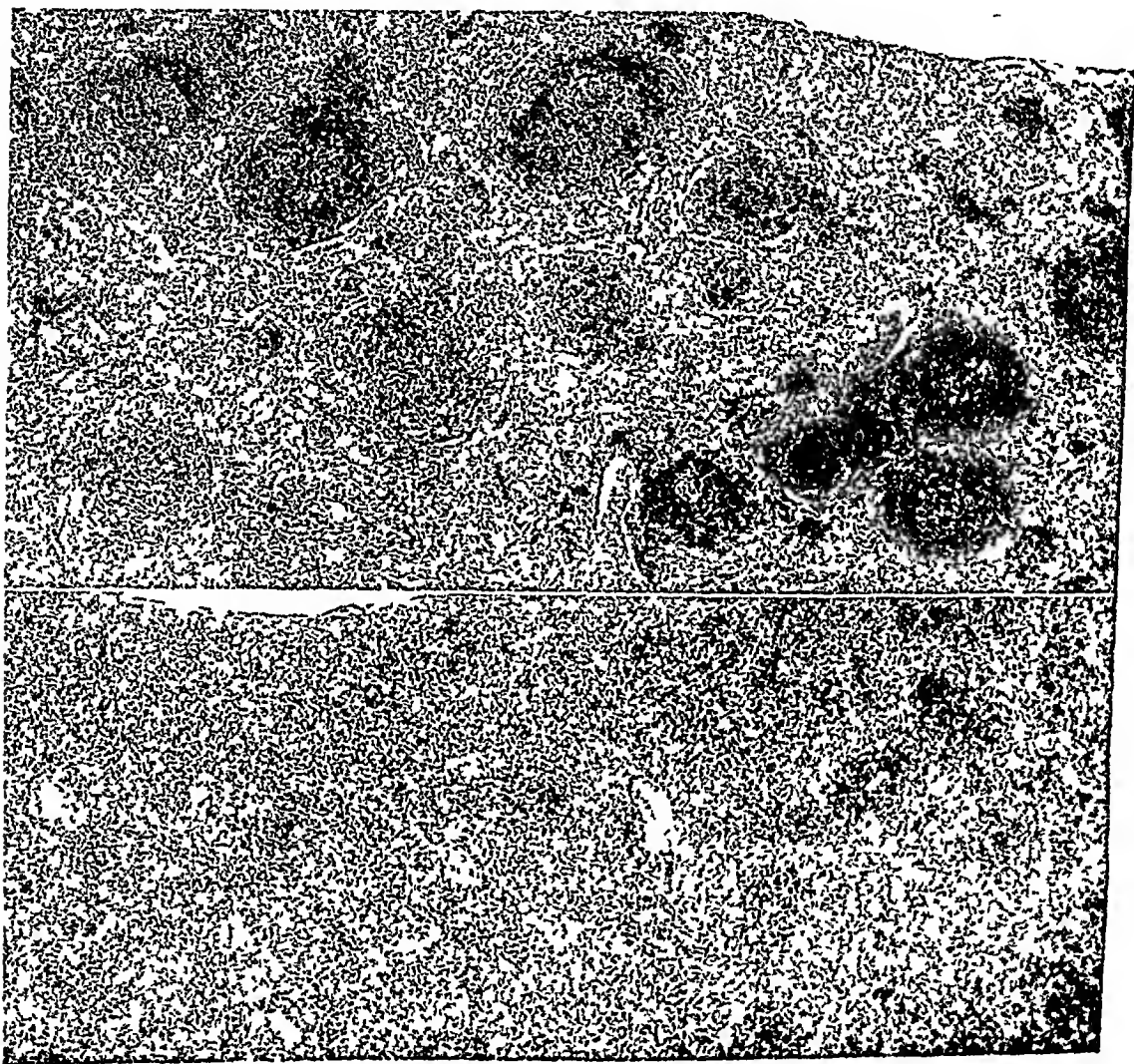


FIG 1 Comparison of spleen from guinea pig given extract of urine from normal individual (above) with spleen from guinea pig given extract of urine from patient with chronic myeloid leukemia (below). Low power, 27 X.

Histological changes, in contrast, were marked, and supplied the criteria for judging the degree of myeloid change present.

Figure 1 is a low power comparison of the spleen of an animal showing the myeloid change with that of an animal not showing such a change. The loss of prominence of follicular structure is at once apparent. Figure 2 is a higher power view to show the general nature of the cellular response in the spleen. The myeloid change is produced by the presence of cells, including blasts, myelocytes, and adult polymorphonuclear neutrophils.

Cells undergoing mitotic division are present, as are also multinuclear giant cells, histologically identical with megakaryocytes

The bone marrow of animals showing the myeloid reaction contained an increased number of immature granulocytes. In many instances there were also present increased numbers of immature red cells. There was a

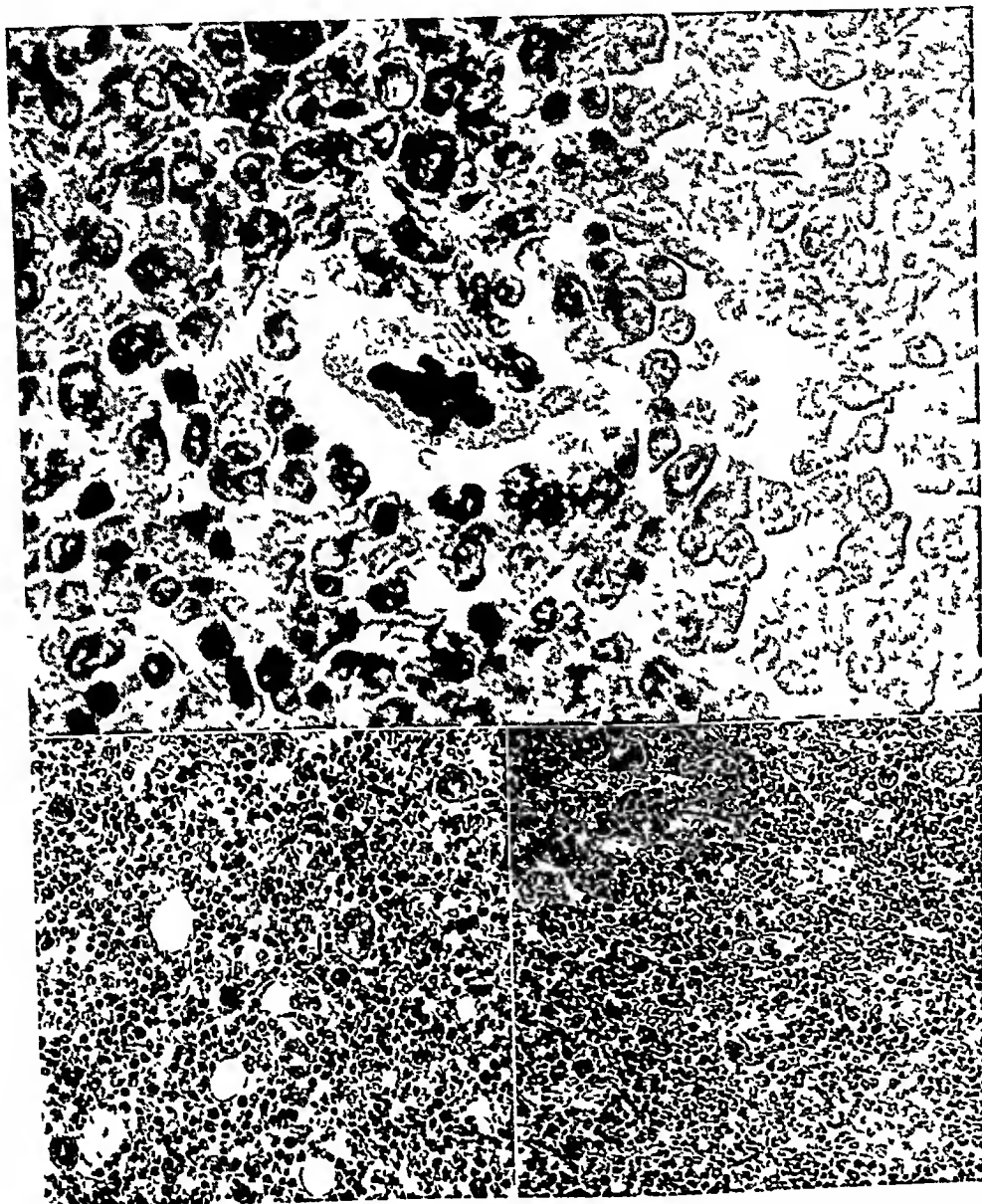


FIG 2 (above) Spleen from guinea pig given extract of urine from patient with chronic myeloid leukemia showing presence of immature myeloid cells and megakaryocyte. High power, 590 \times

FIG 3 (below) Tibial bone marrow from guinea pig given extract of urine from normal individual (left) and from guinea pig given extract of urine from patient with chronic myeloid leukemia (right) to show decreased amount of fat and increased cellularity. Low power, 158 \times

compensatory reduction of fat Figure 3 is a low power comparison of the femoral marrow of an animal receiving extract of urine from a normal individual Figure 4 shows high power views of unfixed marrow imprints

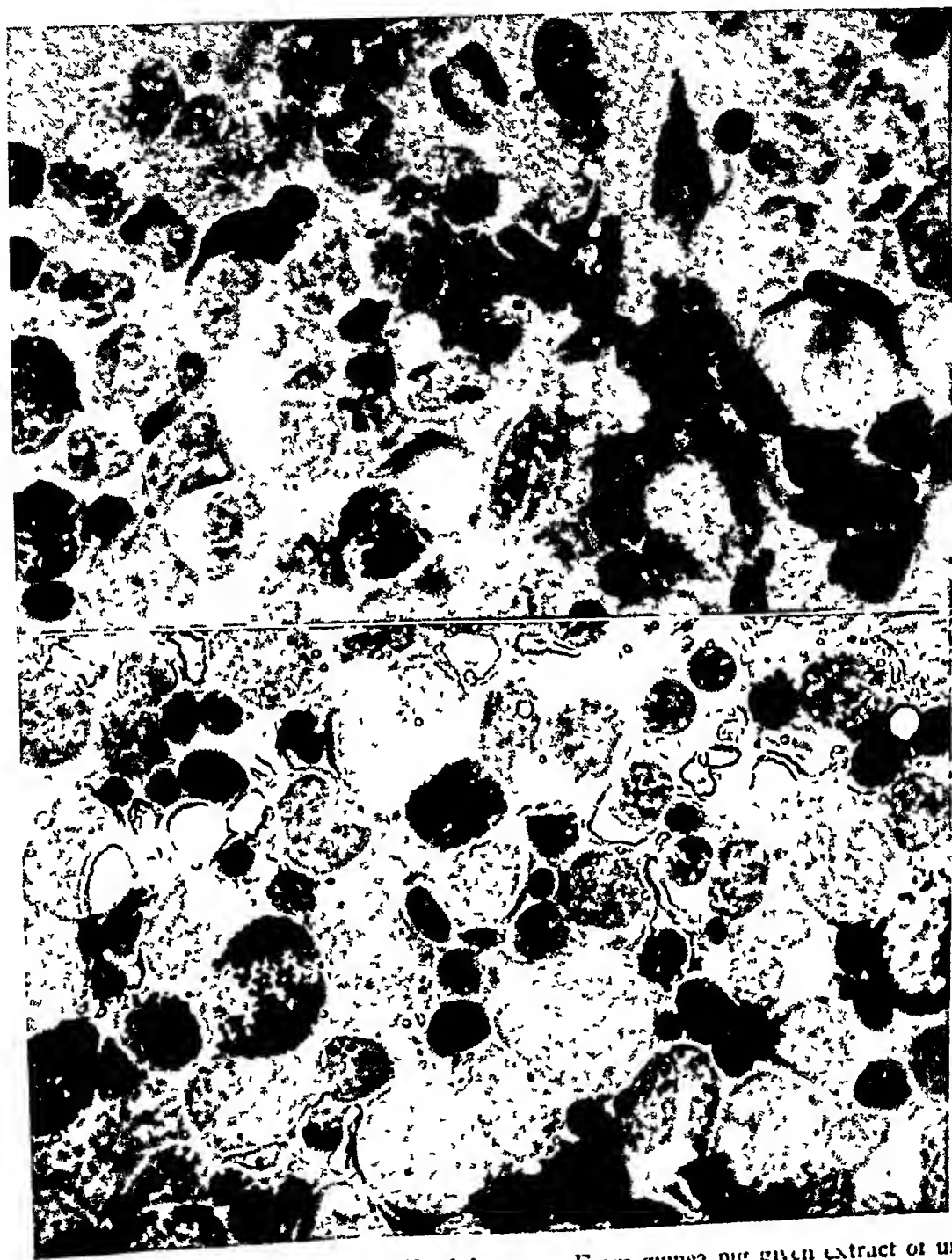


FIG 4 Bone marrow imprints, Wright's stain From guinea pig given extract of urine from normal individual (above) and from guinea pig given extract of urine from patient with chronic myeloid leukemia (below) High power, 800 \times

These changes in the spleen and bone marrow were the most constant, and no animal was considered to show the myeloid response unless they were

present to some degree. Other organs frequently showed myeloid metaplasia, however.

Figure 5 shows the liver of an animal showing myeloid metaplasia. The abnormal cells were typically found in perivascular and periportal sites and



FIG 5 Section of liver from guinea pig given extract of urine from patient with chronic myeloid leukemia showing myeloid infiltration in periportal area. Two cells in mitosis (M) are visible. High power, 1000 X.

consisted of mature and immature granulocytes, including blast cells and cells undergoing mitotic division.

Myeloid metaplasia frequently occurred in the suprarenal gland where

it was found in the cortex, immediately beneath the capsule, and between the cords of cortical cells. Figure 6 shows an area of adrenal cortex containing mature and immature granulocytes.

Another observation of interest was that the lungs of guinea pigs receiving extracts of urine from normal people or patients with chronic lymphoid leukemia, showed a considerable amount of lymphoid activity

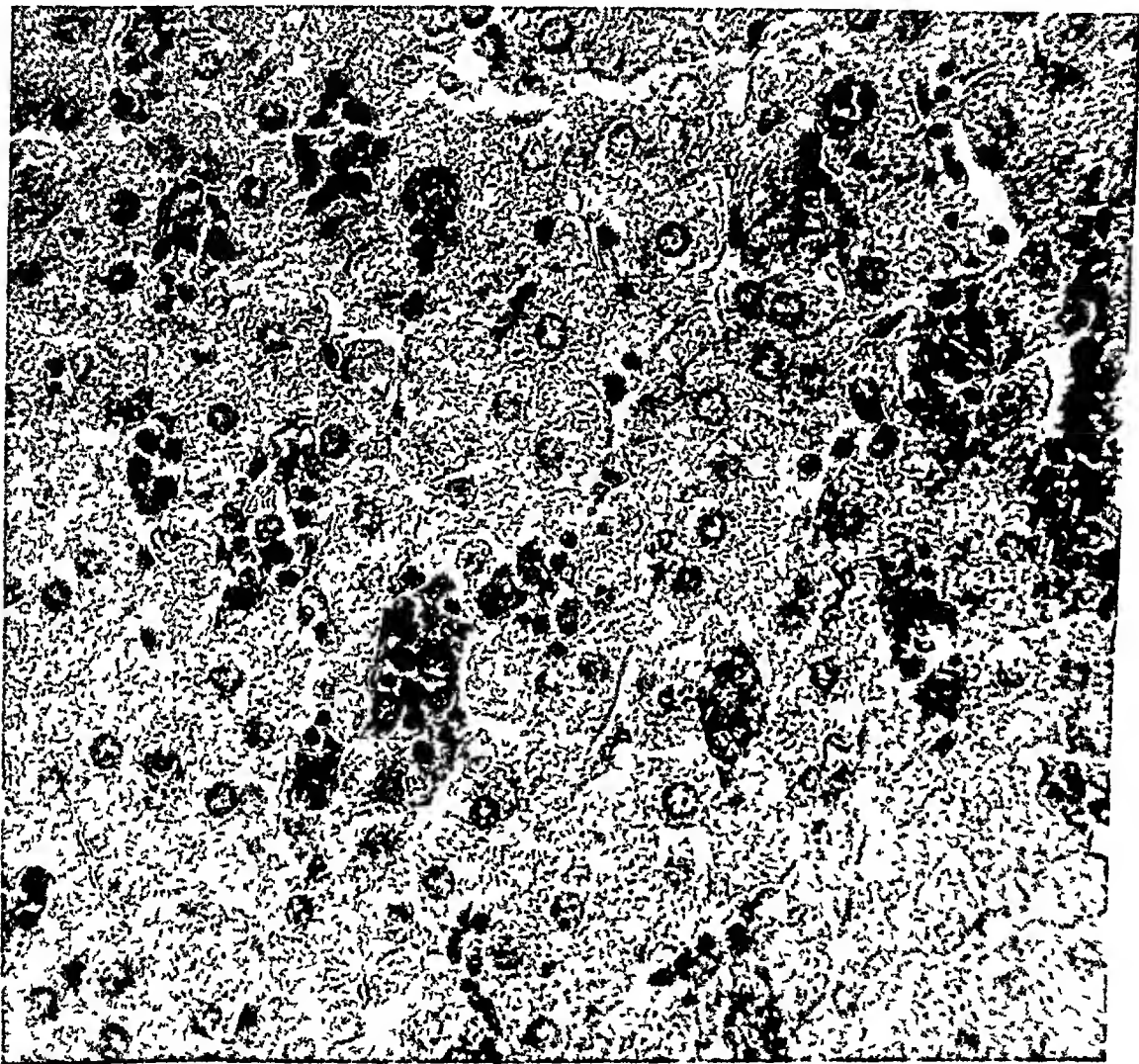


FIG 6 Section of suprarenal cortex from guinea pig given extract of urine from patient with chronic myeloid leukemia showing infiltration with myeloid cells. High power, 590 \times .

around small, peripheral blood vessels. In such animals there was a cuff of mature and immature lymphocytes around nearly every vessel. This is shown in figure 7. In animals showing the myeloid response, such lymphoid activity was absent or greatly diminished. This is shown in figure 8. A similar state of affairs existed in the kidneys. Guinea pigs receiving extract of urine from normal individuals or patients with chronic lymphoid leukemia had kidneys which contained a variable number of small mononuclear cells,

presumably lymphocytes, in the spaces between the glomeruli and proximal convoluted tubules. Kidneys from guinea pigs showing the myeloid response did not contain such cells.

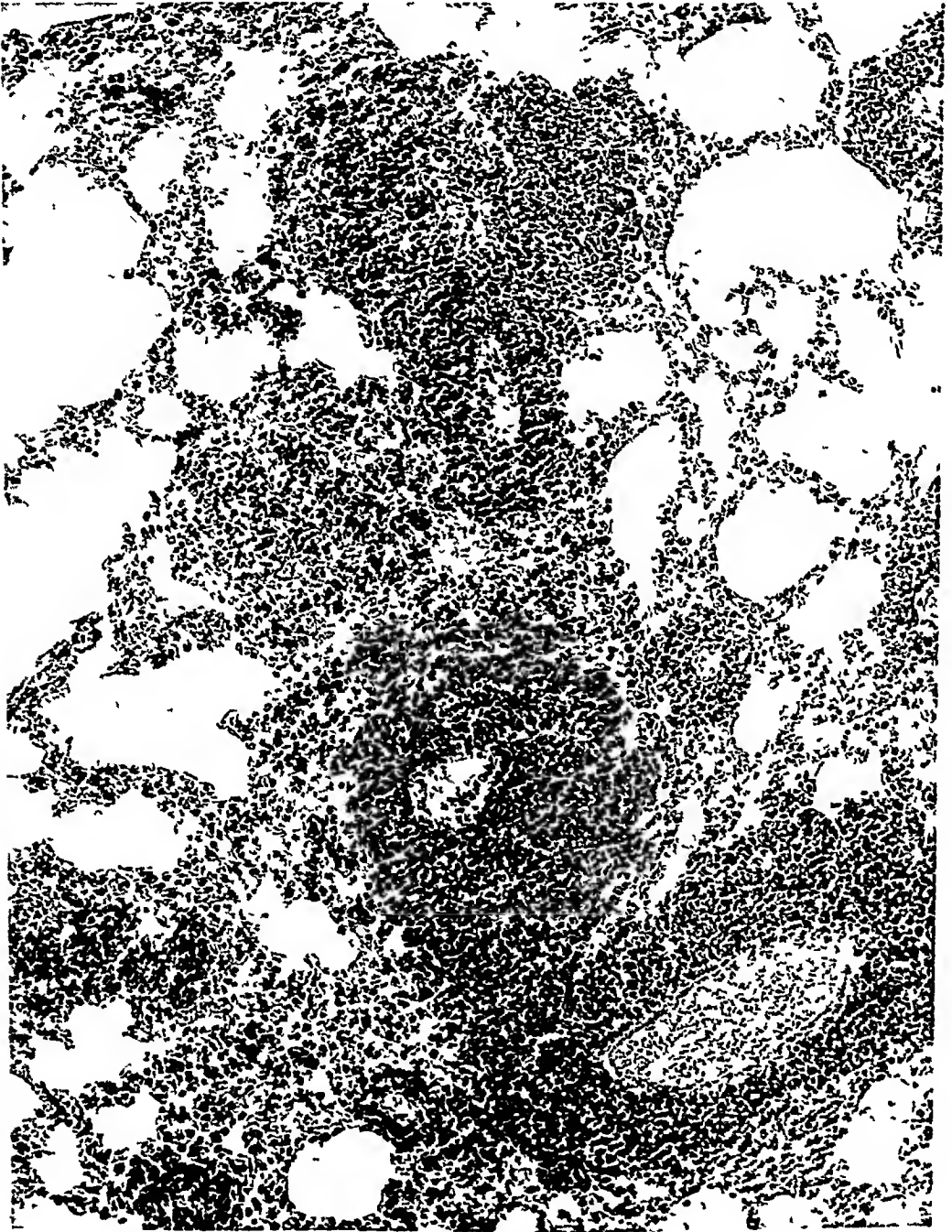


FIG 7 Section of lung from guinea pig given extract of urine from patient with chronic lymphoid leukemia showing large numbers of mature and immature lymphocytes surrounding blood vessels at periphery of lung. Extract of urine from normal individuals produces a similar picture. Low power, 135 X

The lymph nodes did not participate in the myeloid metaplasia. Guinea pigs showing myeloid hyperplasia and metaplasia generally had normal appearing, inactive nodes, as compared with the more active lymphoid tissue of other guinea pigs.

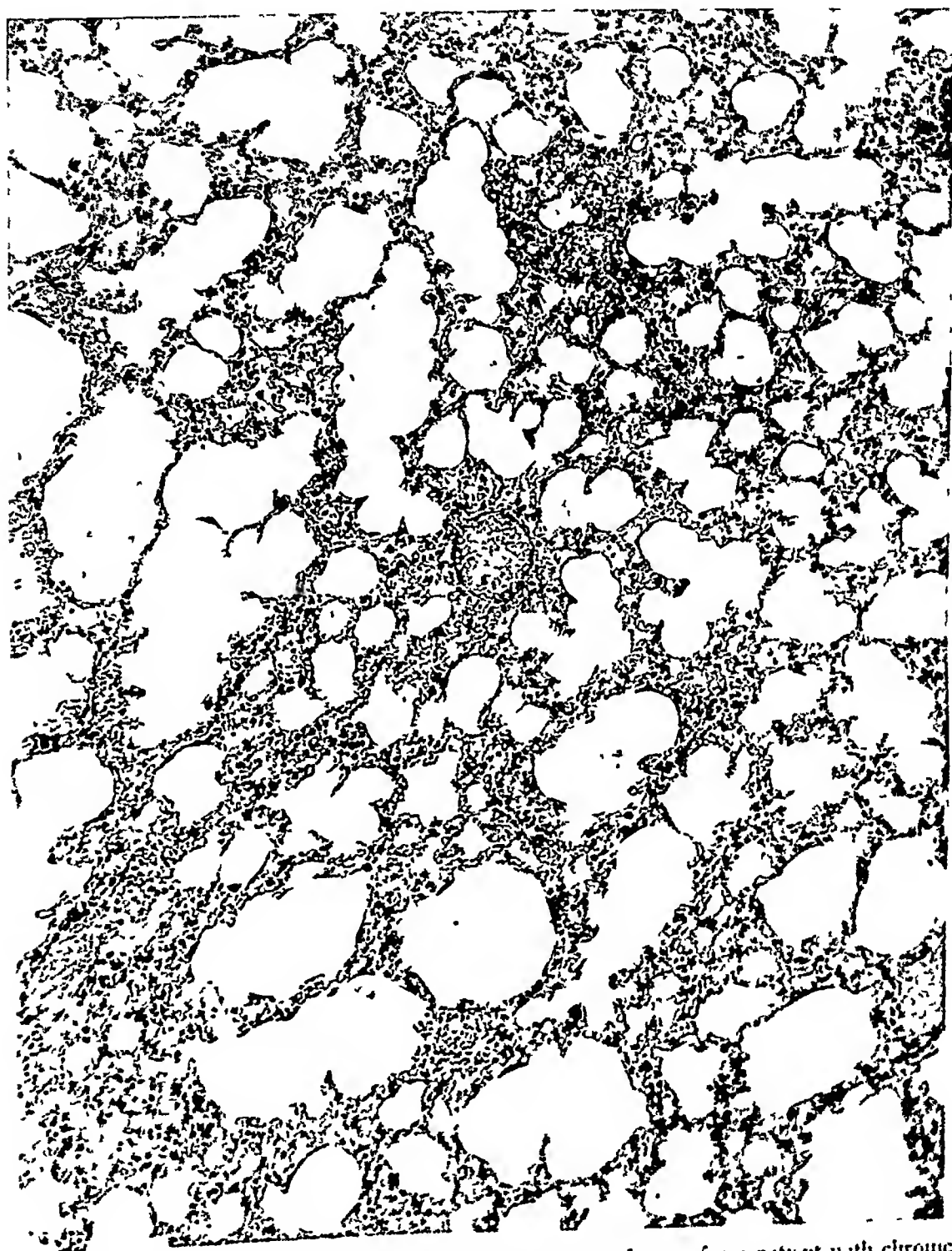


FIG 8 Section of lung from guinea pig given extract of urine from patient with chronic myeloid leukemia to demonstrate absence of lymphoid activity. Compare with figure 7. Low power, 135 X

For purposes of classification in discussing the various extracts, the myeloid reaction just described has been graded as +++, ++, +, and \pm , depending upon the degree of change present. A +++ response indicates changes in all of the organs as described above whereas a \pm response indicates changes only in the spleen and marrow and such changes, although qualitatively identical with those described, are quantitatively less.

The classification of "erythroblastic" is included in the charts. Animals in this group showed large numbers of nucleated red cells in the organs of the hematopoietic system. When the reaction was less marked, the normoblast was the predominant cell. When the reaction was greater, large numbers of true blast cells (presumably megaloblasts) were found in association with the more mature normoblasts. Such cells were present in spleen, liver, marrow and suprarenal glands. There was no disturbance of the granulocyte series in these animals, the reaction apparently being limited to the erythrocyte series. The significance of the reaction is not entirely clear but we believe it represents a non-specific stimulation which occurs because of a peculiar susceptibility in certain of the guinea pigs.

Animals not having any of the characteristics listed above were classified as negative.

Results with Kaolin Extract **Method** This method was adapted from that described by Houssay and Biasotti.³ Urine was obtained from patients with chronic myeloid leukemia, chronic lymphoid leukemia, Hodgkin's disease, acute monocytic leukemia, multiple myeloma, infectious mononucleosis, carcinomatosis, and from normal individuals. Eight to 10 liters were extracted at one time. Enough concentrated HCl was added to make the pH approximately 1.5 using thymol blue as an indicator. The acidified urine was placed in a five gallon carboy and 10 grams of colloidal kaolin (Merck) were added per liter of urine. The carboy was agitated vigorously once or twice an hour for about eight hours. It was then placed in a cold room (40 to 50° F) overnight to allow the kaolin to settle. The supernatant urine was removed by siphon and about one liter of water added and mixed with the kaolin. This mixture was filtered on a Buchner funnel with suction until the kaolin was only damp. Sixty-six per cent alcohol, 100 c c per original liter of urine, was then added to the kaolin and was mixed thoroughly four or five times during the next two hours. The alcohol was separated from the kaolin on a Buchner funnel with suction and the kaolin discarded. The clear, brown, alcoholic solution was placed in an evaporating dish and the alcohol evaporated in a fan blast at room temperature. After the alcohol had evaporated, an acid insoluble precipitate formed. Enough 10 per cent sodium hydroxide was added to adjust the pH to 7.5 to 8.0 using brom-thymol blue as an indicator. The addition of the alkali dissolved the precipitate completely. Distilled water was added so that 1 c c of the extract represented 33 c c of original urine. The extract was passed through a Berkefeld V filter and stored in sterile bottles.

This material was injected subcutaneously into guinea pigs in doses of 4 to 10 c.c. daily, most animals receiving two doses of 4 c.c. daily. Many of the animals receiving this extract of urine made from patients with chronic myeloid leukemia died between the fifth and eighth week of injection. If death had not occurred by the tenth week, the animals were generally sacrificed. A few were maintained for longer periods. Animals receiving extracts of urine from patients not having chronic myeloid leukemia generally remained well.

The results obtained with this extract are shown in table 1. The myeloid leukemia urine extract produced myeloid change with greater frequency than did the other types of urine extracts, 13 of 26 animals showing such myeloid reaction. Two of 15 animals receiving normal urine extract showed a + myeloid response and two animals receiving urine extract from a patient with multiple myeloma showed weakly positive myeloid reactions. One animal

TABLE I
Results Obtained with the Kaolin Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodgkin's Disease	Acute Monocytic Leukemia	Multiple Myeloma	Miscel- laneous
Myeloid reaction							
+++	8						
++	4						2
+	1		2			1	
±						1	
Erythroblastic	1	1					
Negative	12	5	13	2	2		3

receiving urine extract from a patient with infectious mononucleosis and another animal receiving urine from a patient with aplastic anemia showed strong positive myeloid reactions. These two animals are included under miscellaneous in table 1. Three other animals receiving urine extracts from patients with polycythemia rubra vera and carcinomatosis did not show positive myeloid reactions. Two of the 15 guinea pigs receiving urine extract from normal individuals showed a positive myeloid response. None of the six animals receiving extract of urine from chronic lymphoid leukemia patients had a positive myeloid reaction.

Benzoic Acid Extract Method: This method was adapted from that described by Katzman and Doisy.⁴ Urine was collected from patients with chronic myeloid leukemia, chronic lymphoid leukemia, acute monocytic leukemia, and from normal individuals and preserved with chloroform (10 to 20 c.c. per liter). Glacial acetic acid was added in sufficient quantity to reduce the pH to 4-5 using methyl red-methylene blue as an indicator. The acidified urine was filtered through coarse paper and the precipitate discarded. A saturated solution of benzoic acid in acetone was added to the filtered urine in amounts of 50 c.c. per liter, with vigorous stirring. The benzoic acid pre-

precipitated immediately, and after a short time allowed for settling was separated by filtration on a Buchner funnel. To the benzoic acid was added a volume of acetone equal in volume to that in which the benzoic acid was originally dissolved. The acetone insoluble material was allowed to settle out and most of the supernatant material was siphoned off. The remainder, including the precipitate, was separated by centrifuging. The precipitate was washed five times with acetone to remove the remaining benzoic acid. The precipitate was next washed three times with distilled water (using 25 c c of water for each liter of urine unless larger amounts of urine were handled at one time. In the latter event, we used 300 to 500 c c distilled water per 100 liters of urine). This preparation yields the material soluble in an acid medium and was found to have little or no activity when administered to animals. The precipitate was resuspended in a small amount of water and the pH adjusted to 7.5-7.8 by the addition of 5 per cent sodium hydroxide and final volume was adjusted so that 1 c c of the solution re-

TABLE II
Results Obtained with the Benzoic Acid Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Acute Monocytic Leukemia
Myeloid reaction				
+++	3			
++	2			
+	1	1	1	
±	1	1		1
Erythroblastic	1	1	1	
Negative	4	5	1	1

presented 333 c c of original urine. The material was centrifuged to separate any insoluble material still remaining. The supernatant fluid, which was now a clear, dark brown solution, was put in sterile bottles and 0.5 per cent phenol added as a bacteriostatic. No infections resulted in the animals injected with this material.

Extracts prepared by this method were obtained from the urines of patients with chronic myeloid leukemia, chronic lymphoid leukemia, acute monocytic leukemia, and from normal individuals. They were administered to guinea pigs in progressive daily doses of 0.25 c c to 1.5 c c. This extract usually caused death of the animals within two weeks of the beginning of the injections, and the total amount of original urine necessary to produce a positive result was less than that required in other extracts. Extract from only 3.24 liters of urine from patients with chronic myeloid leukemia was sufficient to produce positive myeloid reactions, on the average.

Results obtained with this extract are shown in table 2. Seven of 12 animals receiving the extract of urine from patients with chronic myeloid leukemia showed positive myeloid reactions, five of which were strongly

positive Two of eight animals given extract of urine from patients with chronic lymphoid leukemia showed weakly positive myeloid reactions as did one of three animals receiving extract of urine from normal individuals One of two animals receiving extract of urine from a patient with acute monocytic leukemia also showed a positive myeloid reaction The erythroblastic response was obtained in three animals

Chloroform Extracts Method. Urine was obtained from patients with chronic myeloid leukemia, chronic lymphoid leukemia, Hodgkin's disease, acute monocytic leukemia, acute blastic leukemia (type unidentified) and from normal individuals Insofar as possible, urine from several patients with the same disease was pooled until enough was obtained to make extract for the entire series of animals In this way, a homogeneous extract was prepared and it was certain that all animals were receiving identical material Urine was strongly acidified by adding 250 cc of concentrated HCl per 1750 cc of urine It was boiled in open beakers for at least 10 minutes to hydrolyze The hydrolyzed urine was then extracted in a continuous chloroform extractor Urine flow was adjusted so that about one liter of urine passed through the extractor each hour The urine entered the lower end of the extraction column and was discarded from the top The chloroform, after condensing in the reflux type condenser, was broken into small droplets by a fused ground glass disk inserted in the tube which admitted the chloroform to the extraction column The chloroform collected in the lower end of the extraction column and returned to the flask as a result of the hydrostatic pressure maintained in the extraction column Practically no difficulty with emulsions was encountered when working with these strongly acid urines

If the urine was less strongly acid (pH 3.5, for example), emulsions with chloroform were produced which were best broken up by placing a constant temperature water bath (60° C) around the lower end of the extraction column

After the urine had been extracted, the chloroform extract was distilled at atmospheric pressure on a water bath to a convenient volume Usually, 20 liters of urine were extracted with 300 to 500 cc of chloroform, and the final chloroform extract was distilled to 100 to 150 cc in volume

This chloroform extract was extracted five times with 50 cc portions of 10 per cent sodium hydroxide in order to remove components soluble in strong alkali This should, theoretically, have removed the acids and phenols, leaving the neutral substances in the chloroform

The remaining chloroform fraction was placed in a sterile suction flask and enough sterile sesame oil added so that after removal of the chloroform 1 cc of the oil preparation was derived from approximately 5,000 cc of urine Chloroform was removed by applying suction to the flask, the incoming air being filtered through a sterile Berkefeld filter The preparation was dark, reddish brown in color and was not a complete solution Some of the solid material slowly settled out so that it was necessary to shake the

bottle vigorously before administration. This oil extract contained the chloroform soluble, alkali insoluble fraction of the urine extract.

The five 50 c c portions of 10 per cent sodium hydroxide were pooled and the pH adjusted to approximately 1.0 by the addition of concentrated HCl. This caused a heavy precipitate to form. It was evaporated to dryness on a steam bath. The dry material was ground up and extracted five times with 50 c c of chloroform. This made it possible to free the mixture of the salt present. The chloroform extract was passed through coarse filter paper to remove particulate matter and the paper washed with small amounts of chloroform until no brown color remained. It was placed in a sterile suction flask equipped with a Berkefeld filter and evaporated to dryness. Enough sterile water and 10 per cent sodium hydroxide were added to adjust the pH to about 8.0 and the final volume so that 1 c c represented 200 c c of original urine. This fraction contained the chloroform and alkali soluble fractions of the urine.

TABLE III
Results Obtained with the Chloroform Soluble and Alkali Insoluble Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodgkin's Disease	Acute Monocytic Leukemia	Acute Leukemia
Myeloid reaction						
+++	1					
++	2					
+						
±	2					
Negative	7	9	7	4	2	1

A Results with Chloroform Soluble Alkali Insoluble Extract The oil preparation was given to guinea pigs as shown in table 3. It was administered subcutaneously in daily doses of 0.1 c c (representing 500 c c of urine) in most instances. A few animals received twice this amount. Injections were continued for eight weeks after which time the animals were sacrificed. Only a very few animals died spontaneously and anemia did not develop. A few of the animals lost weight. Twelve guinea pigs received extract of urine from patients with chronic myeloid leukemia. Five showed positive myeloid reactions and seven were negative. Of these negative animals, three received an extract which had been standing at room temperature for two months. Whether or not deterioration took place cannot be stated, but such a possibility exists. All the animals receiving extracts from sources other than patients with chronic myeloid leukemia were negative. It is noteworthy, perhaps, that this particular extract produced no erythroblastic reactions.

B Results with Chloroform and Alkali Soluble Extract The alkali soluble fraction of the chloroform extract was administered subcutaneously to guinea pigs, shown in table 4, in daily doses of 1-2 c c (representing 200 to

400 c c of original urine) The usual plan was to start with doses of 1 c c and increase to 2 c c after seven to 10 days. Injections were continued for eight weeks, after which the animals were sacrificed. Several animals receiving the extract of urine from patients with chronic myeloid leukemia died spontaneously before the end of the eight-week period. Some of these animals developed mild anemia and several lost weight.

Six of the 14 animals receiving the extracts from patients with chronic myeloid leukemia showed positive myeloid reactions. Two guinea pigs showed the erythroblastic response and six were negative. Of the animals receiving the extract of urine from patients with chronic lymphoid leukemia, one showed a positive myeloid reaction, two showed the erythroblastic reaction, and 11 were negative. Eleven animals received extract of urine from normal individuals. Four of these showed positive myeloid reactions, one of which was strongly positive, the other three less so but none the less definitely positive. Seven were negative. Of the nine animals receiving extract of urines from patients with Hodgkin's disease, four showed a response which has been listed as "unclassified positive." This reaction differed from those previously described. The organs of these animals contained large numbers of megakaryocytes with an associated cellular reaction consisting of large numbers of blast cells, unassociated with any obvious erythropoietic hyperactivity. Numerous adult eosinophiles were present. This reaction involved especially the spleen, suprarenal gland cortex, and bone marrow. One of the nine animals had a weakly positive myeloid reaction.

TABLE IV
Results Obtained with the Chloroform and Alkali Soluble Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodgkin's Disease	Acute Monocytic Leukemia	Acute Leukemia
Myeloid reaction						
+++	1		1			
++	1					
+	2	1	2			
±	2		1	1		
Unclassified positive				4		
Erythroblastic	2	2			2	1
Negative	6	11	7	4	2	1

and four were negative. Six other animals receiving urine extract from a patient with acute leukemia, type unidentified, and a patient with acute monocytic leukemia, did not show any myeloid response.

Combined Results Table 5 is a composite of tables 1 to 4, showing results obtained with different extracts of urine from patients with the specified diseases and from normal individuals. A total of 64 guinea pigs received extracts of urine from patients with chronic myeloid leukemia of which 31 (48.5 per cent) showed definite myeloid hyperplasia and metaplasia.

Twenty-nine animals were negative and four showed the erythroblastic response

One hundred and four guinea pigs received extracts of urine from individuals not having chronic myeloid leukemia. Of these, only 16 (15.4 per cent) showed any evidence of myeloid reaction. Three of these were strongly positive myeloid reactions, including one animal each receiving urine extract from a normal individual, from a patient with infectious mononucleosis, and from a patient with aplastic anemia.

TABLE V
Composite of Tables 1 to 4, Showing Combined Results Obtained
with All Types of Urine Extracts

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodg- kin's Disease	Acute Mono- cytic Leukemia	Acute Leukemia	Multiple Myeloma	Miscel- laneous
Myeloid reaction								
+++	13		1					
++	9							2
+	4	2	5				1	
±	5	1	1	1	1		1	
Unclassified positive				4				
Erythroblastic	4	4	1			1		
Negative	29	26	28	10	7	2		3
Total	64	33	36	15	8	3	2	5

DISCUSSION

We believe these data indicate that urine from patients with chronic myeloid leukemia contains some substance which is capable of producing myeloid hyperplasia and metaplasia in guinea pigs. Extracts of urine from individuals not having chronic myeloid leukemia do not produce a similar response with as great frequency.

Various extraction methods were effective in recovering this substance from urine. Attempts to separate the chloroform extract into alkali soluble and insoluble fractions, using 10 per cent sodium hydroxide, did not result in complete separation, since both fractions contained activity. The alkali soluble fraction produced a greater number of positive reactions, but those animals which showed positive myeloid reactions after injection with the alkali insoluble fraction, did so with extract derived from a smaller amount of urine. It seems likely, therefore, that the methods employed thus far have failed to separate the active substance into any single fraction.

In earlier reports^{1,2} and reports of Miller et al.,⁵ it was thought that extracts of urine from patients with chronic lymphoid leukemia produced changes in guinea pigs which could be considered lymphoid hyperplasia and possibly metaplasia. In this series of experiments, however, we have been unable to detect any difference between the results obtained with lymphoid leukemia urine extracts and normal urine extracts. Many of the animals

receiving such urine extracts had spleens in which the follicles were large, spreading, and active, producing an appearance of mild hyperplasia. The extracts of normal urine, however, produce just as much such change as do the extracts of urine from patients with chronic lymphoid leukemia. The lymphoid change present is not comparable in amount to the myeloid changes observed in animals with the myeloid reaction. Any lymphoid hyperplasia resulting in our animals, therefore, does not appear to be specific nor limited to animals receiving extracts of urine from chronic lymphoid leukemia patients. Extracts of urine from patients with the other diseases have not shown any consistent activity so that the results obtained with chronic myeloid leukemia urine extracts appear to be specific.

A few positive myeloid reactions did occur in animals injected with extracts of urine from individuals not having chronic myeloid leukemia. Such positive reactions, however, were not, with one or two exceptions, as marked as those obtained with extracts of urine from patients with chronic myeloid leukemia nor did they occur with as great frequency.

The most reasonable explanation for the occurrence of these "false positive" reactions is that all urine contains some of the substance which is present in larger amounts in urine of patients with chronic myeloid leukemia. Several experimental variables, thus far not controlled, would affect the response of guinea pigs to this substance. These include individual animal susceptibility, variation in the manufacture of the extracts, and variations in individuals from whom the urine was obtained. If a combination of these variables happened to be favorable, it may be expected that a relatively small amount of the substance can produce a positive myeloid reaction.

The substance which produced the myeloid reaction has not been identified. It was recovered by methods known to be capable of obtaining certain of the products of the glands of internal secretion from urine. Androgens, estrogens, adrenal cortical hormone, and pituitary substances can be recovered by one or more of the methods employed. Because the chloroform extraction method is capable of recovering androgens from urine, 12 guinea pigs were given testosterone propionate in varying doses without the occurrence of a positive myeloid reaction. Other guinea pigs receiving whole anterior pituitary extract similarly did not develop myeloid changes.

Whether the substance is a normal metabolic product present in excess in the urine of chronic myeloid leukemia patients or whether it is an abnormal product not normally present in urine remains to be seen. If it is an excess of a normal substance, such excess might be due to overproduction of the substance or to decreased production of some normal neutralizing substance.

Further investigations, aimed at securing a more purified and concentrated product, are in progress so that quantitatively greater reactions can be produced in animals and chemical identification of the substance can be made. Separation of the various extracts into more specific fractions is

being attempted now. In the event that all the activity can be isolated in one fraction, a better understanding of the chemical nature of the substance will be at hand.

SUMMARY

1. Extracts of urine from patients with chronic myeloid leukemia produced myeloid hyperplasia and metaplasia in guinea pigs with much greater frequency than did extracts of urine from patients not having chronic myeloid leukemia.

2. Three different extraction methods and four different extracts are described.

3. The nature of the substance and plans for further investigation are discussed briefly.

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SULFADIAZINE; FURTHER CLINICAL STUDIES OF ITS EFFICACY AND TOXIC EFFECTS IN 460 PATIENTS *

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EVIDENCE for the effectiveness of sulfadiazine in many of the common bacterial infections has now been obtained in several large clinics by a number of observers, all of whom have attested to the relatively low toxicity of this drug ^{1, 2, 3, 4, 5}. Since the time of our earlier publication on this subject,² the use of sulfadiazine at the Boston City Hospital was limited largely to those groups of cases in which additional data seemed desirable. In this paper we wish to summarize the past year's experience with the clinical use of sulfadiazine at this hospital and, in so doing, to bring out a number of points of interest concerning its efficacy and toxicity.

The clinical material comprises 460 patients, none of whom was included in the previous report. Almost all of them were adults treated on the medical wards. For the most part they included patients with streptococcal, staphylococcal and gonococcal infections, the bacterial meningitides and infections of the urinary tract. In such cases sulfadiazine usually was used only if other sulfonamides had not been given for the immediate illness. Sulfadiazine was also used from the start in patients known to have or suspected of having renal impairment, and it was used to continue treatment when toxic effects resulted from other sulfonamides (mostly sulfathiazole) and further chemotherapy was deemed necessary or desirable. All patients who received sulfadiazine for less than 24 hours or a total dose of less than 10 grams are excluded. Most of the latter had mild infections, but a few of them received a small amount of the drug a few hours before death.

The distribution of cases according to age is shown in table 1. A large proportion of the patients were in the higher age groups. One-third of those who recovered and two-thirds of those who died were over 50 years old.

In general, the drug was given orally, beginning with a 4-gram dose followed by 1 gram every four hours, and this was often reduced to 1 gram every six hours after the temperature had remained normal for a day or two. In the cases of meningitis and in some others with severe infections the initial dose was 5 grams of the sodium salt given parenterally, and this was often followed by two or more doses of one-half that amount at suitable intervals.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

This study was carried out with the generous cooperation of the staffs of the various clinical and laboratory services throughout the hospital. The sulfadiazine was supplied by the Lederle Laboratories, Inc.

in an attempt to maintain blood levels between 15 and 20 mg per 100 c c. In such patients oral doses were also adjusted to maintain high levels until the infection was completely controlled. Fluids were given liberally, usually about 3 liters a day, and more when the larger doses were used, but it was not always possible to control this factor adequately and probably this accounted for some of the renal complications to be mentioned later. The total dose, of course, varied widely, as shown in table 2. About one-third of the patients

TABLE I
Age Distribution of Patients Treated with Sulfadiazine

Age Group (years)	No of Cases	Recovered	Died
Less than 20	51	48	3
20-29	63	58	5
30-39	91	83	8
40-49	80	77	3
50-59	73	59	14
60-69	62	50	12
70 and over	40	27	13
Total	460	402	58

TABLE II
Total Dose of Sulfadiazine Used

Dose (grams)	No of Cases	Died
15-19	42	5
20-29	109	10
30-39	88	3
40-49	73	11
50-74	70	13
75-99	35	5
100-149	22	4
150-249	11	5
250 or more	10	2
Total	460	58

received less than 30 grams, another third got between 30 and 50 grams, and the rest were given larger amounts over periods ranging from 10 days to more than five months.

CLINICAL RESULTS

A summary of the various types of cases treated and a rough estimate of the therapeutic response to sulfadiazine is given in table 3. A few remarks concerning the salient features of each of the groups of cases may be pertinent.

Hemolytic Streptococcal Infections There were 98 such cases, including two with meningitis (which are listed lower down in the table), but excluding the cases of endocarditis. These cases are of particular interest,

since the clinical data on the effect of sulfadiazine on hemolytic streptococcal infections are notably scant in the reports thus far available

A favorable therapeutic response was obtained in every one of the 56 cases of erysipelas. Fever and pulse rate returned to normal in almost every instance within 24 to 48 hours after the first dose was given, and this was

TABLE III
Summary of Results of Sulfadiazine Therapy in Various Infections

Infection	No of Cases	Died	Evaluation of Therapy			Average Dose (grams)	
			++	+	0	Recovered	Died
Hemolytic streptococcal infections							
Pneumonia	6	0	6	0	0	48	—
Tonsillitis, peritonsillitis, etc	28	0	25	3	0	27	—
Erysipelas (mostly facial)	56	2	52	4	0	25	41
Sepsis	6	1	5	0	1	46	12
Subacute bacterial endocarditis	14	9	1	1	12	106	131
Staphylococcal infections							
Pneumonia	12	0	12	0	0	35	—
Sepsis	5	0	1	4	0	147	—
Friedlander's bacillus infection							
Pneumonia, Type A	2	0	2	0	0	135	—
Pyelonephritis and liver abscesses, Type B	1	1	0	0	1	—	125
Gonococcal infections							
Genital	6	0	6	0	0	58	—
Arthritis acute	16	0	13	3	0	71	—
Arthritis chronic	2	0	0	2	0	350	—
Bacterial meningitis							
Meningococcus	11	0	11	0	0	73	—
Meningococcemia without meningitis	4	0	4	0	0	45	—
Pneumococcus	8	5	3	2	3	254	140
Streptococcus	2	0	2	0	0	56	—
Influenza bacillus, Type B	1	0	1	0	0	55	—
Colon bacillus	1	0	1	0	0	20	—
Miscellaneous	1	2	1	0	3	23	30
Urinary tract infections							
Acute	39	1	33	6	0	41	41
Chronic	21	4	3	15	3	84	38
Pneumococcal pneumonia	80	6	66	12	2	42	52
Pneumonia, etiology undetermined	75	12	45	17	13	39	43
Chronic pulmonary infections	26	6	5	8	13	13	52
Miscellaneous infections, not listed elsewhere	31	9	4	17	13	71	59
Totals	160	58	302	94	64		

++ Good therapeutic response attributable to sulfadiazine

+ Doubtful result or good response with relapse

0 No apparent beneficial effect attributable to sulfadiazine

accompanied by rapid improvement in the local lesion. Relapse of infection occurred a week or more after discharge from the hospital in four of the erysipelas patients who had been treated for only three or four days, but all four of them responded favorably to a second course of the same drug. In three patients who failed to respond to several days' treatment with sulfadiazole, a rapid drop in fever and clearing of the local lesion occurred.

within 24 hours after the sulfathiazole was withdrawn and sulfadiazine substituted in the same doses. Two deaths occurred in patients in whom the erysipelas lesion was improved. One patient, 62 years old, died of a cerebral hemorrhage two weeks after drug therapy was stopped, the other, 84 years old, died of renal complications of therapy and will be referred to later.

In the six patients with pneumonia, the hemolytic streptococci were obtained from the sputum only, but they were present in large numbers and in repeated specimens as the only significant pathogen. None had a bacteremia. A sterile effusion was demonstrated in one case after several days of treatment. The response in five of these cases was similar to that usually observed in favorable cases of pneumococcic pneumonia. The sixth patient was extremely ill and had definite renal impairment and congestive cardiac failure before treatment was begun. This patient had a stormy course for several days, after which recovery from the infection was complete.

Rapid and complete recovery was also the rule in the 28 cases of severe tonsillitis. These included five cases with a complicating peritonsillar or cervical abscess and four with sinusitis at the time treatment was begun. The six cases of "sepsis" included one with portal vein thrombosis, two with cellulitis and wound infections, and three which followed abortions. One of the latter patients died in less than 36 hours after receiving only 12 grams of drug, mostly as the sodium salt intravenously. In the others the infection cleared rapidly. The general impression was gained that the results of treatment with sulfadiazine in all the cases of hemolytic streptococcic infections were definitely superior to those obtained from any of the other sulfonamides previously used.

Subacute Bacterial Endocarditis The results of treatment in 14 cases were, on the whole, quite disappointing. The one patient who was apparently cured had rheumatic heart disease, and one blood culture was positive for alpha hemolytic streptococcus before treatment was begun, but there had been no evidence of embolic phenomena. This patient became afebrile directly after treatment, and numerous subsequent cultures showed no growth even after the drug was discontinued. In one other patient, a few negative blood cultures were obtained during therapy but subsequent ones were positive again. No favorable effects of treatment were noted in any of the remaining patients, although the drug was tolerated well in most instances over long periods during which high blood concentrations were maintained. The organism was a beta hemolytic streptococcus in one patient, who died after a week of therapy. In one other patient the streptococcus was identified as an enterococcus belonging to the group D, the rest were classified either as *Streptococcus viridans* or as alpha hemolytic streptococci.

Staphylococcal Infections *Staphylococcus aureus* infections of the lungs have been seen in this hospital with more than the usual frequency since the outbreak of influenza of 1940-1941.¹ Twelve such cases were treated with sulfadiazine since our previous report.² *Staphylococcus aureus* was the only or predominant organism in repeated specimens of sputum from all these

cases and was obtained from blood cultures in three patients. The organism was coagulase-positive in each instance. The response to chemotherapy was rapid in every case and recovery occurred without complications. Only one of these patients received the chemical for more than one week. Sulfathiazole was not used in any of these cases.

Of the five patients with staphylococcus "sepsis," only one became afebrile rapidly after treatment with sulfadiazine and excision of a subcutaneous abscess. Another patient with bacteremia and pyelonephritis improved slowly but continued to have pyuria. The other three continued to have positive blood cultures under full doses of sulfadiazine and their blood was rendered bacteria-free only after surgical drainage of foci of osteomyelitis. In two of the latter cases, longer courses of treatment with sulfathiazole likewise failed to influence the bacteremia prior to operation.

Friedländer's Bacillus Infections Two patients with severe acute pneumonia whose sputum yielded Type A Friedländer's bacilli in almost pure culture responded to treatment with sulfadiazine with a rapid drop in temperature and marked clinical improvement. The blood cultures were negative in both of these cases. A third patient, not listed in the table, had a fulminating pneumonia and bacteremia with the Type A organism. He died within 12 hours after beginning treatment and less than 48 hours after the supposed onset of his disease. He had received a total dose of 10 grams of sodium sulfadiazine intravenously and 3 grams of sulfadiazine orally without apparent effect on the downhill course*. One patient with pyelonephritis, from whose urine and blood Type B Friedländer's organisms were cultured, had a stormy course and failed to improve under sulfadiazine therapy. In this case the same organism was found in multiple liver abscesses at autopsy.

Gonococcal Infections The six patients with gonococcal infections of the genital tract all responded to sulfadiazine treatment with a prompt subsidence of fever, symptoms and discharge. Included among them were two patients with epididymitis, two with orchitis, and one with conjunctivitis in addition to the acute urethritis. The sixth patient had cervicitis and salpingitis. There were no relapses noted.

Among the 18 patients with gonococcal arthritis, six also had active genital infections at the same time. Positive cultures were obtained before treatment in every case from the synovial fluid or from the urethra or cervix or both. In 13 of the cases with acute arthritis, fever and the acute joint symptoms subsided within one to five days and did not recur. Three of the acute cases and both of those with symptoms of several weeks' duration responded more slowly and continued to have fever and joint pains with some

* Recently a fourth patient with severe type A Friedländer's pneumonia, with bacteremia and involvement of one entire lung, showed a very good response to intensive treatment with sulfadiazine. Bacteremia and toxemia subsided rapidly, but there was extensive necrosis of a large part of the affected lung which required surgical drainage. The patient improved after the operation, but the ultimate result is still in doubt.

swelling for several days. In five of the patients with acute arthritis, treatment with full doses of sulfathiazole for 10 days or longer failed to bring about improvement, and the fever and joint symptoms subsided within 24 to 48 hours after sulfadiazine was started. In three of these cases, the possibility of drug fever was eliminated by permitting an interval of two or more days to elapse during which fever and arthritis were unabated while no sulfonamides were given.

Bacterial Meningitis Clinical data concerning the efficacy of sulfadiazine in such cases are also meager, and further information is highly desirable. The cases included here were studied more directly by Dr. Dingle and his associates and only a few high lights of the results of sulfadiazine treatment need be mentioned. There were 27 cases of bacterial meningitis and four cases of meningococcemia without clinical or laboratory evidence of meningitis in which sulfadiazine was the only sulfonamide used. In the latter and in all the 11 cases of meningococcus meningitis, a rapid and complete cure was effected. Similar results were obtained in a three and one-half year old patient with Type B influenza bacillus meningitis, in a five week old infant with colon bacillus meningitis, and in two patients with streptococcal meningitis, one two months and the other four months old. The latter four patients and one of those with meningococcal meningitis were the only patients under 14 years old who are included in this report.

All the eight patients with pneumococcal meningitis received homologous type-specific antipneumococcus serum, usually within eight to 24 hours after sulfadiazine treatment was begun. Three of the eight patients recovered, of these, two were over 60 years old and one had a bacteremia which recurred during treatment. Pneumococcal endocarditis was found at autopsy in two of the cases and was probably present in a third fatal case with rheumatic heart disease on which autopsy was not done. In the other two fatal cases there were extensive fractures of the skull.

The miscellaneous cases of meningitis include one in which no bacteria were identified but the clinical picture and the favorable response to sulfadiazine treatment suggested a probable meningococcal etiology. Two of the other three cases turned out to be tuberculous and the third syphilitic in origin, and no improvement occurred under sulfadiazine therapy.

Urinary Tract Infections There were 60 patients, in addition to the two already mentioned, who were treated with sulfadiazine for a variety of infections of the urinary tract. The results were essentially similar to those previously noted.² In general, the patients with uncomplicated acute infections responded very favorably. Two instances of acute glomerular nephritis of moderate severity are included. They showed definite improvement under treatment.

Almost all of the chronic cases were associated with local surgical conditions or with severe systemic diseases which obscured the results of therapy or tended to maintain the infection. Some of these patients had unpaired

renal function with nitrogen retention before treatment was begun. This was definitely improved in most instances during treatment, but in two patients the blood non-protein nitrogen increased. All of these patients required the closest control of their fluid balance and chemotherapy. The deaths among these cases resulted from the underlying local or systemic disease.

Pneumonias The results of sulfadiazine treatment in the 80 cases of pneumococcal pneumonia which are included here compare favorably in every respect with those previously reported from this and from other clinics^{1, 2, 3, 5}. Of the six deaths in this group, five occurred in patients in whom the pneumonia was secondary to a disease which was itself fatal. In the pneumonias of undetermined etiology, the results varied. In about two-thirds of these cases the response to the chemotherapy was comparable to that seen in typical pneumococcal pneumonia, which some of them may have been. Those who failed to show any favorable response to the treatment include a few atypical pneumonias, possibly of virus etiology, and others that were secondary to severe systemic disease. The latter accounted for most of the deaths in this group.

Chronic Pulmonary Infections These included 26 cases of lung abscess, bronchiectasis, putrid empyema and pulmonary tuberculosis. Five patients in this group showed rapid and marked improvement following sulfadiazine treatment with subsidence of fever and considerable clearing of the pulmonary signs in spite of the underlying chronic lesion. It was assumed that these favorable results were due to the effect of the drug on a superimposed acute pulmonary infection, the etiology of which could not be determined. A few of the remaining patients in this group showed some gradual improvement of pulmonary or bronchiectatic abscesses under prolonged chemotherapy.

Miscellaneous Conditions These included a large variety of febrile diseases, most of which are not usually considered to be definite indications for sulfonamide therapy. Only two patients in this group are worth mentioning. One was a patient with two large suppurative lesions of actinomycosis, one of the jaw and the other of the lung and thoracic wall. This patient was failing steadily and his disease was extending during several weeks of treatment with sulfanilamide and sulfathiazole, but slow and steady improvement began under intensive and continued treatment with sulfadiazine over a period of five months. The lesions have apparently healed completely and have remained so during the three months since the drug was discontinued. The second patient had severe Ludwig's angina and showed a dramatic response within 24 hours after beginning intensive sulfadiazine therapy. No radiation or surgery was employed in these two cases.

* Subsequently, however, this patient developed active pulmonary tuberculosis, with positive sputa for tubercle bacilli, but actinomycetes could no longer be obtained in smears or culture. The cervical and chest wall lesions remained healed.

TOXIC EFFECTS

Untoward symptoms or laboratory evidence of toxicity from sulfadiazine in general were infrequent and mild. Table 4 contains a summary of their incidence and of the average amount of drug received by the patients having each of the various toxic manifestations.

Nausea and vomiting were notably mild and uncommon, and in no instance interfered with continued oral therapy. The 23 patients listed included six who vomited only once, two in whom the symptom may have been due to other causes (over-digitalization in one and mesenteric thrombosis in the other) and two in whom it began during sulfathiazole treatment and con-

TABLE IV
Summary of Toxic Effects Attributable to Sulfadiazine in 460 Cases*

Toxic Effect	No. of Cases	Per cent	Average Total Sulfadiazine Therapy	
			Grams	Days
Nausea and/or vomiting	23	5.0	49	8
Leukopenia (drop below 4,000)	3	0.7	120	21
Rash with or without fever	7	1.5	62	11
Episcleritis	1	0.2	92	15
Fever alone	1	0.2	40	7
Psychosis (?)	2	0.4	29	5
Urinary tract complications				
Crystalluria only	34	7.4	72	15
Hematuria, all cases	24	5.2	106	17
Gross, with colic	4	0.9	41	6
Microscopic	20	4.3	120	20
With crystalluria	11	2.4	159	27
Without crystalluria	13	2.8	65	11
With oliguria	3	0.7	22	4
Increase in blood nonprotein nitrogen †	6	1.3	94	15

* There were no instances of cyanosis, anemia, purpura,⁷ hepatitis, arthralgia, or peripheral neuritis attributable to sulfadiazine.

† Rise of more than 30 mg per 100 ml. One of these patients had hematuria and is included above.

tinued after sulfadiazine was substituted. In 20 other patients in whom sulfadiazine was substituted because of vomiting from sulfathiazole, the nausea and vomiting subsided promptly. Of interest are six patients with active peptic ulcers who all received a full course of sulfadiazine for various infections and whose gastric symptoms improved during this treatment.

Leukopenia One patient with cirrhosis of the liver and jaundice, who received a total of 156 grams of sulfadiazine in 25 days, had a drop of leukocytes from 18,000 to 650 per cubic millimeter with complete absence of granulocytes and with marked thrombocytopenia. In this patient, treatment was continued for five days after the leukocyte count had reached 2400, and the level of free sulfadiazine was 25.6 mg per 100 cc of blood on the day after the drug was discontinued. Recovery was complete following withdrawal of the drug and administration of fluids, transfusions and pent-

nucleotide * In two other patients the leukocyte count had dropped appreciably at the time the drug was discontinued, namely to 3500 on the seventeenth day in one and to 2500 on the eighteenth day in the other. There were more than 30 per cent granulocytes in both instances and no special treatment was necessary. In five other patients leukocyte counts below 4000 were noted during the first few days of sulfadiazine treatment, but these were attributable to the underlying disease and did not interfere with further chemotherapy.

Drug Fever, Episcleritis and Dermatitis Drug fever and episcleritis without other manifestations were each encountered in one case. The episcleritis was reactivated after 6 grams of the same drug were given 12 days later. A dermatitis from sulfadiazine occurred in seven patients. It was scarlatiniform in three cases and maculopapular or morbilliform in the others. It was accompanied by a low-grade fever in all but one instance. In one of the patients the rash appeared on the twenty-second day, after 135 grams of the drug, whereas in the others it became manifest between the seventh and eleventh days, after total doses of 35 to 66 grams. In one of the patients in whom a maculopapular rash appeared on the eleventh day, and in another who developed a scarlatiniform eruption on the seventh day of sulfadiazine treatment, this drug was used to continue chemotherapy without interruption after a febrile reaction with erythema nodosum occurred from sulfathiazole. This reaction had completely subsided during the second day on sulfadiazine. Although the latter drug was used in the same manner and with the same or larger total doses in 21 patients having fever and rashes from sulfathiazole therapy, these were the only two among them who also showed the same toxic effects after receiving sulfadiazine.

Nervous and Mental Manifestations Because of the frequency with which psychoses from sulfadiazine were noted by other observers,^{1,3} this manifestation was looked for particularly. There were only two patients in whom mental symptoms might have been attributable to sulfadiazine. One severe alcoholic patient treated for pneumonia had slight fever and delirium on the seventh day of therapy, but this did not recur when a dose of 5 grams of the same drug was given three days later. A second patient, admitted for smoke inhalation and mild pulmonary infection, was disoriented and confabulated on the third day after receiving 18 grams of sulfadiazine; the total drug concentration in the blood at the time was 16 mg. per 100 ml. The symptoms cleared promptly when the drug was withdrawn. No patient in the present series developed peripheral neuritis from sulfadiazine.

Anemia and Hepatitis No instance of anemia or hepatitis was noted. On the other hand, six patients with severe liver damage and one with severe hemolytic anemia received doses of from 40 to 156 grams of sulfadiazine without any further deleterious effect on the liver or on the anemia. Indeed, liver function tests indicated improvement in these cases.

* This case has been reported in greater detail by Dr. J. J. Curr.¹²

Complications in the Urinary Tract These are the most frequent of the significant untoward manifestations of sulfadiazine therapy. They deserve special emphasis not only for that reason, but also because their more serious effects are largely preventable by proper adjustment of the fluid and drug intake.

A large variety of crystals of sulfadiazine and its derivatives, some of which were similar in form to those described by Lehi and Antopol,⁸ were noted in routine urine examinations in 34 of the cases without other abnormal findings. Included among them were some patients who had been vomiting and a number who had received alkali (sodium bicarbonate) with each dose of drug.⁹ No significance was attached to this isolated finding provided that the urinary output was adequate. In almost all such instances the crystals appeared only after the urine had been permitted to stand at room temperature for several hours, but they were not often seen in the freshly voided specimens.

Hematuria, as evidenced by the finding of a few red blood cells in the microscopic examination of the sediment in routine urinalysis, was noted in 20 patients. In some of these patients the finding may have resulted from previous catheterization or from the underlying disease, as in the cases of bacterial endocarditis. In such instances the hematuria was not accompanied by crystalluria. In one of the patients with blood but no crystals in the urine, there was a marked temporary decrease in urinary output on the third day of sulfadiazine therapy. This patient had had a febrile reaction with urinary suppression and retention of nonprotein nitrogen in the blood from a previous course of sulfathiazole that had ended only five days before the sulfadiazine was given. A second patient had a temporary decrease in urinary output associated with congestive failure, accompanying streptococcic pneumonia.

In four patients, hematuria was associated with costovertebral angle pain and tenderness, or with typical ureteral colic. In two of these patients, one with gross and the other with microscopic hematuria, this was associated with a low fluid intake and with a high concentration of drug in the blood. In both instances hematuria and pain subsided when the fluid intake was increased. A third patient, who had received a course of sulfathiazole therapy without untoward events several months earlier, experienced typical ureteral colic and allegedly passed a stone on the sixth day of sulfadiazine treatment. The calculus was not seen, but there was transient gross hematuria without crystalluria for two days, which then cleared although the sulfadiazine therapy was continued in the same dosage throughout this time and for four days thereafter. The fourth case will be referred to in more detail further on.

It is of interest to note that varying degrees of hematuria were present in 11 of the patients in this series before the sulfadiazine was begun. These included two cases of acute glomerular nephritis. In nine of these cases,

including both of the latter, the hematuria cleared or decreased while the patients were taking full doses of sulfadiazine and maintaining high blood levels. The hematuria did not increase during treatment in the other two patients.

Significant increases in the level of the non-protein nitrogen of the blood occurred during sulfadiazine treatment in five patients who had essentially normal levels to begin with, and in a sixth patient who had a high level before treatment was begun. In one of these patients, who had malignant hypertension, the non-protein nitrogen rose from 40 to 120 mg per 100 c c and the total sulfadiazine level reached 28 mg per 100 c c, of which only 7 mg were in the "free" form. In a second patient, a rise in the non-protein nitrogen from 30 to 67 was accompanied by a rise in the total drug level to 30 mg per 100 c c, of which only 13 were "free." In three of the other patients the higher drug level reached was only 18 or less, and only 2 or 3 mg were in the conjugated form. In fact, in all the chemical determinations of sulfadiazine in the blood in the present series of cases, large amounts of the conjugated form were found only in the two cases cited.

It is of interest here, also, that 14 other patients had high levels of non-protein nitrogen (between 50 and 100) before sulfadiazine treatment was started. In 10 of these cases there was a significant drop in this level, often to normal, during the course of the chemotherapy, whereas in the other four it was not materially affected. In four of these patients the blood concentration of the drug rose to levels between 22 and 40 mg per 100 c c, but only a small part of this was not in the "free" form.

A Fatal Case of Urinary Suppression with Colic, Hematuria and Azotemia from Sulfadiazine. One patient died, presumably of a renal complication. Since this was the only fatality attributable to sulfadiazine in the present series, a few of the relevant details in this case may be of interest.

A woman 84 years old was treated with sulfadiazine in the routine manner for facial erysipelas. The fever subsided rapidly and the facial lesion showed marked improvement within two days. The drug was stopped on the fourth day, after the patient had received a total of 22 grams. The non-protein nitrogen on admission was 30. Specimens of urine taken on admission, on the day when the drug was stopped and two days later all revealed no abnormal finding. It was only on the afternoon of the latter day, when the patient complained of definite symptoms suggesting right ureteral colic, that attention was called to the fact that the patient's urine output had been very low. A small amount of "smoky" urine filled with red blood cells and crystals was voided at that time. During the next two days the patient passed only a few cubic centimeters of similar urine and the non-protein nitrogen of the blood rose steadily to 97 mg per 100 c c. Cystoscopy and catheterization of the ureters were then carried out, and revealed no obstruction, only a small amount of bloody urine with few crystals of drug were found in the bladder. The drug level at this time was only 2 mg per 100 c c of blood, and two urine specimens each showed a total of only 60 mg of sulfadiazine per 100 c c, of which all but 10 mg were in the conjugated form. Administration of fluids by mouth and parenterally was then of no avail and the patient died on the following day. A few concretions were found in the kidney pelvis at autopsy.

Five other similar cases of urinary suppression under sulfadiazine therapy have already been reported,^{2, 10, 11, 12, 13} two of which were fatal¹³ The other three were all in young adults in whom increase in the fluid intake and early ureteral catheterization resulted in complete relief *

DRUG TOXICITY IN PATIENTS RECEIVING MULTIPLE COURSES OF SULFONAMIDE THERAPY

The effect of previous sulfonamide therapy on the toxicity during readministration of the same or related compounds is of great interest, and few data on this subject are available Lyons and Balberor¹⁴ observed febrile reactions in 36 per cent of patients on readministration of sulfathiazole, but sulfanilamide or sulfapyridine did not precipitate a fever when given after sulfathiazole They did, however, observe some patients who had early sulfathiazole fever after having previously been treated with one of the other two drugs Since a large number of the patients in the present series had more than one course of sulfonamide therapy during the same or on separate admissions, the toxic effects from the sulfonamides in these cases will be reviewed briefly

Readministration of Sulfadiazine Fifteen patients in this series each received two courses, and six received three courses of treatment with sulfadiazine The average total dose was 48 grams given in about eight days during the first course, 58 grams in 11 days during the second, and 42 grams in seven days during the third The average interval was 12 weeks between the first and second courses and three and one-half weeks between the second and third courses Except for transient microscopic hematuria during the first course in one instance, no toxic effects from sulfadiazine were noted

Among these 21 patients, 10 had also been treated with sulfathiazole 5 once, 4 twice and 1 on three occasions In the latter five patients the courses of sulfathiazole were alternated with those of sulfadiazine One had a rash and fever from a single and initial course of sulfathiazole, another had a rash and fever during the second course of this drug, and in three others it gave rise to nausea and vomiting each time it was taken In addition, one of these patients developed a severe anemia during an earlier course of sulfanilamide and another had intense vomiting during a previous course of sulfapyridine therapy

Sulfadiazine in Patients Who Had Other Sulfonamide Drugs Without Toxic Effects Thirty-six patients in the present series received a course of another sulfonamide drug without untoward effects during the same or a separate hospital admission In 25 cases it was given before and in 11 cases after the course of sulfadiazine Sulfapyridine was used in two, sulfanilamide in five, and sulfathiazole in 29 cases, and one of the latter received

* Two further cases of urinary suppression have been reported since this paper was submitted One of them required nephrostomy¹⁶ and the other recovered after ureteral catheterization¹⁷

two courses The total dose of these drugs varied from 15 to 600 grams, but it was less than 35 grams in most instances The average dose of sulfadiazine in these cases was 69 grams, given in 12 days The interval between the courses of the drugs was one week or less in 20 cases and varied from four weeks to four years in the others One of the patients had a rash and fever from sulfadiazine on the ninth day after receiving 56 grains, another had crystalluria, and a third, already noted, had hematuria and ureteral colic and presumably passed a calculus during the course of sulfadiazine therapy

Sulfadiazine in Patients Who Experienced Toxic Effects from Other Sulfonamides In addition to the various cases already mentioned, 14 patients who received sulfadiazine had a febrile reaction, with or without a rash, from some other sulfonamide drug within 10 days to two years These included three who had a rash and fever with each of two courses of sulfathiazole, one who had fever alone during one course and a rash during another, both with sulfathiazole, three who had a rash only during the second of two courses of this drug, one who had a febrile reaction from two different courses of sulfanilamide and a rash after a course of sulfathiazole, one who had a moderate anemia from sulfanilamide on one occasion and a rash from sulfathiazole on another, and one who had a scarlatiniform rash from sulfanilamide Almost all of these patients received 30 grams or more of sulfadiazine without toxic effect beyond a transient microscopic hematuria in two cases

Complications in the urinary tract from other sulfonamides, mostly sulfathiazole, were noted in 17 of the patients Three of them had nitrogen retention of significant degree, eight had hematuria, and six had crystalluria One of these patients had a diminished urinary output during sulfadiazine, but none of the others showed any toxic effects from the latter drug

Two additional patients had severe anemia during sulfanilamide treatment more than one year prior to receiving sulfadiazine, and 17 others had nausea and vomiting during treatment with sulfapyridine or sulfathiazole, or both, more than one month previously Among the latter, one experienced nausea, another had oliguria and slight hematuria, and a third had a rash during treatment with sulfadiazine

SUMMARY AND CONCLUSIONS

The results of treatment with sulfadiazine in 460 patients with a variety of infections are presented These are in addition to the 446 patients previously reported from this hospital The earlier conclusions concerning the efficacy and low toxicity of sulfadiazine have been confirmed and extended

In particular, the additional data presented suggest that sulfadiazine may be accepted as the drug of choice in all cases of hemolytic streptococcal infections and in all of the various acute bacterial meningitides.

The accumulated clinical results in the cases of acute gonococcal and staphylococcal infections and in the acute infections of the urinary tract suggest that the efficacy of sulfadiazine in most of these cases is probably similar to that of sulfathiazole. Because of its lower toxicity, however, sulfadiazine may be considered to be the drug of choice, particularly when prolonged therapy is desirable.

The present results, taken together with others reported,^{1, 2, 3, 5, 6b} seem to justify the claim for sulfadiazine as the drug of choice for initiating chemotherapy in all cases of acute pulmonary infections and for continuing treatment in such cases when they are caused by pneumococcus, streptococcus and probably also staphylococcus and Friedlander's bacillus.

Toxic effects attributable to sulfadiazine were relatively few and mild. The comparatively frequent occurrence of complications in the urinary tract warrants the exercise of caution in the control of the dosage of the drug in relation to the fluid intake and output. This is particularly essential in old persons, in patients with hypertension, and in every patient who may have some impairment of renal function. With adequate control, this drug may be administered so as to produce therapeutically effective blood levels wherever indicated, even in many patients with severe renal disease. When oliguria occurs, the fluid intake should be increased promptly or the dose of drug reduced, depending on the circumstances. If there is marked or complete suppression of the urine output, particularly when accompanied by ureteral pain, fluids should be forced and ureteral catheterization should be employed early if a fatal outcome is to be avoided. A fatal case of urinary suppression with ureteral colic, hematuria and azotemia is reported.

The occurrence of agranulocytosis after prolonged therapy in one case suggests that, regardless of how infrequent this complication may be, it must be looked for in all patients undergoing sulfadiazine treatment for two weeks or more. Early recognition, with prompt withdrawal of the drug, will probably avoid fatalities from this complication.

Full courses of sulfadiazine have been used in a considerable number of patients who had previously been treated with sulfonamide drugs. The toxic effects from sulfadiazine in these cases were apparently similar in frequency and in all other respects to those seen in patients who had no previous experience with other sulfonamides. This was true regardless of whether or not the patients had experienced toxic effects from the latter.

No evidence of "sensitization" was noted in any of the 21 patients who received a second or third course of sulfadiazine. In most of these cases full doses were used for a week or more each time. Some of them had also received one or more courses of other sulfonamides, with or without toxic effects. The possibility of sensitization, however, has not been excluded. Episcleritis was reactivated on early readministration of sulfadiazine in one case. Other instances of rashes and febrile reactions reappearing when the drug is given again after a brief interval have also been known to occur, although they were not encountered in the present cases.

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CONTROL OF THE HYPERGLYCEMIA OF OBESE "DIABETICS" BY WEIGHT REDUCTION *

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THREE years ago we¹ reported the favorable effect of weight reduction upon the hyperglycemia of obese middle-aged persons. We are now in a position to deal with a still larger material. The effect of reduction of weight upon the delayed utilization of glucose displayed by 62 obese adult men and women forms the substance of this paper. A number of the patients had been referred to the Diabetic Clinic by their physicians because diet and insulin had failed to abolish the glycosuria. Others came to the hospital because they were suffering from pruritus vulvae, cataract, gangrene, gall-bladder disease or merely the fatigue and breathlessness which often accompany obesity. A few of these latter patients knew that the urine had contained sugar for many years. Others had been told that they were diabetic within the recent past. Still others were unaware of the glycosuria until it was noted as part of the routine examination in the hospital. The youngest patient was 27 years of age, the oldest 71 years. The average age of the group was 52 years, and the ages of two-thirds of the patients ranged from 42 to 62. Usually the obesity was not extreme.¹ Two-thirds of the patients were less than 40 per cent overweight. The distribution of the excess weight is shown in table 1. Two-thirds of the patients were females.

TABLE I
Distribution of Excess Weight

Per Cent Overweight	No of Cases
10- 20	5
20- 30	20
30- 40	14
40- 50	8
50- 60	8
60- 70	2
70- 80	1
80- 90	3
90-100	1
Total	62

Since many investigators, including ourselves,² have shown that restriction of dietary carbohydrate results in delayed utilization of glucose, each patient was placed on a standard preparatory diet containing 300 grams of carbohydrate, 80 grams of protein, and approximately maintenance calories for three or more days before the glucose tolerance test was performed. This was important since a number of the patients had been following low

* Read at the St. Paul meeting of the American College of Physicians April 23, 1942

carbohydrate diets as part of the treatment of the diabetes. Others had been eating little because they were ill. The glucose tolerance test was performed in the usual manner, giving $1\frac{3}{4}$ grams of glucose per kilogram of ideal body weight.

The next day, the reduction diet was begun. From then on, the glycosuria was ignored. Insulin was not administered. The patient was prepared for each subsequent glucose tolerance test by feeding the standard preparatory diet containing 300 grams of carbohydrate for five days preceding the test.

The patients need to be separated into two groups in order to judge of results. The first group consists of 47 patients who adhered to the diets

TABLE II
A
Little or No Improvement by Reduction of Weight to Normal

Case No	Age	Normal Weight	First Test					Second Test				
			Wt	F	1 Hr	2 Hr	3 Hr	Wt	F	1 Hr	2 Hr	3 Hr
	Yrs	Lbs	Lbs	Mg %	Mg %	Mg %	Mg %	Lbs	Mg %	Mg %	Mg %	Mg %
209133	58	131	165	300	400	410	370	135	272	371	116	410
451014	43	138	180	270	452	468	480	136	370	524	588	628
407412	46	136	162	186	374	428	404	137	172	292	332	270
284756	52	123	144	252	410	500	480	130	240	306	381	371
474714	71	145	168	245	374	472	482	150	176	290	306	296
140536	41	128	158	264	404	495	602	131	186		360	284

B
Slightly Abnormal Glucose Tolerance Tests after Weight Had Become Normal

400526	45	145	181	124	278	266	176	119	87	200	188	88
422552	61	125	159	254	434	432	378	129	102	220	212	118
412111	12	125	160	258	352	500	310	129	118	190	160	138
411080	57	137	165	176	300	272	211	137	102	212	112	118
373000	62	127	152	152	278	300	278	121	102	208	133	88

prescribed by us as long as we requested them to do so. The second group of 15 patients adhered to reduction diets until they had lost a significant amount of weight, but even though their glucose tolerance tests were still abnormal, they refused to reduce further.

Returning now to the 47 patients who cooperated fully, reduction of weight to normal caused little or no improvement in six of them (12.6 per cent). Their responses are shown in table 2 A. Another five (10.6 per cent) were strikingly improved by reduction of weight to normal. The increase in the ability to dispose of glucose by these patients may be seen in table 2 B which compares the glucose tolerance tests before and after reduction of weight. Further evidence of the marked improvement is had in the fact that diets containing 300 grams of carbohydrate caused neither glycosuria nor abnormally high fasting blood sugars. Each of the remain-

ing 36 patients (76.6 per cent) achieved normal glucose tolerance tests after weight reduction of varying amounts. The tests had become normal in six of these 36 patients when they were still 28 to 45 per cent overweight. However, they had lost 35 to 76 pounds by this time. The remainder of these 37 patients had to continue to reduce their weights to within a few pounds of normal or to fully normal in order to be able to dispose of glucose normally. Mrs. G. C. is an example of how reduction of weight to normal, followed by adherence to that weight, finally made it possible for her to dispose of glucose in an entirely satisfactory manner. Her normal weight was 127 pounds. On February 12, 1940, she weighed 160 pounds and the test was

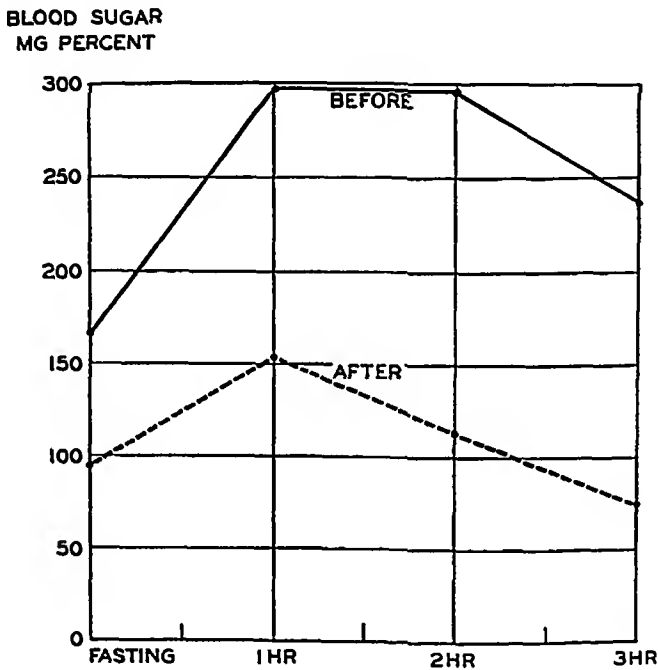


FIG 1

fasting, 182, first hour, 292, second hour, 244, third hour, 250 mg glucose per 100 c c blood. On July 5, 1940, when her weight was 134 pounds, the blood sugar readings during the test were 116, 216, 256, 150. Her weight was 129 pounds on October 14, 1940, and the glucose tolerance test was as follows: 124, 168, 145, 103. One year later, when her weight was the same, the blood sugar readings during the test were 87, 133, 112, 107.

The mean blood sugar readings during the glucose tolerance tests performed before treatment and again when they had become normal after weight reduction are portrayed in figure 1. The distribution of the blood sugar levels during the tests performed before and after weight reduction in these 36 patients is shown in table 3. The effect of weight reduction upon the blood sugar readings obtained in the third hour of the tests is of special interest because the values are so low. Most of them are less than 75 and

five of them are less than 50, suggesting that weight reduction had enabled these patients to dispose of glucose at a supernormal rate

The 15 patients who cooperated partly gave clear evidence that disposal of glucose can be greatly increased by reduction of weight. For example, the patient whose initial glucose tolerance curve was the highest in this group, made the following response to weight reduction. Her normal weight was 133 pounds. Before treatment she weighed 173 pounds and the blood sugar readings of the test performed at that time were: fasting, 212, first hour, 348, second hour, 356, third hour, 500. When her weight had been brought down to 143 pounds, the test gave the following blood

TABLE III

Distribution of Blood Sugars during Glucose Tolerance Tests Performed before and after Reduction of Weight in 36 Patients Whose Tests Became Normal

Blood Sugar	Fasting		First Hour		Second Hour		Third Hour	
	Before	After	Before	After	Before	After	Before	After
Mg %	No	No	No	No	No	No	No	No
25-50								5
50-75		4				2		18
75-100	1	22				10	1	8
100-125	8	10		4	1	12	2	5
125-150	9			14		11	3	
150-175	7			13		1	1	
175-200	3		3	5	5		1	
200-225	2		5		3		3	
225-250	2		4		5		2	
250-275	1		1		4		4	
275-300	1		9		4		1	
300-325	2		5		3		6	
325-350			4		2		2	
350-375			2		4		1	
375-400			1		1			
400-425					1		1	
425-450							2	
450-475					1			
475-500								
500-525			1		1			
525-550			1		1			

sugar values 125, 217, 200, 208. She refused to reduce further. The distribution of the blood sugar values obtained during the glucose tolerance tests performed before and after partial reduction of weight of these 15 patients may be seen in table 4.

Table 5 permits a comparison of the glucose tolerance tests in the several groups of patients. Among the 47 patients who cooperated fully, the sub-group who responded best to weight reduction had the lowest tests, and the sub-group that did not improve had the highest initial test. This suggests that the height of the initial test may be useful as an indicator of the response to reduction. If this is true then the position of the average initial curve from the 15 patients who cooperated only partly permits the prediction

that many of them would have been able to give normal tests if they had lost more weight

TABLE IV

Distribution of Blood Sugars during Glucose Tolerance Tests Performed before and after Partial Reduction of Weight in 15 Patients

Blood Sugar	Fasting		First Hour		Second Hour		Third Hour	
	Before	After	Before	After	Before	After	Before	After
Mg %	No	No	No	No	No	No	No	No
50-75								1
75-100		4						1
100-125	1	6					1	5
125-150	3	4		1				1
150-175	3	1		2		3	1	1
175-200	3	1		2		5	1	3
200-225	1			4		1	2	2
225-250	3		2	3		2	2	
250-275			2	2		1		
275-300	1		1	1	2	3		1
300-325			2		1		2	1
325-350			3		1			
350-375			3		2	1	2	
375-400					1		1	
400-425					2			
425-450			1		1		2	
450-475			1					
475-500					1		1	
500-525					1			
525-550								

TABLE V

Glucose Tolerance Tests on 62 Patients before and after Weight Reduction

		Before				After			
		F	1	2	3	F	1	2	3
Full Cooperation	36 Patients Glucose Tolerance Tests became normal	163	293	292	234	89	154	113	75
	5 Patients Tests became markedly improved	193	328	390	277	102	212	173	116
	6 Patients Tests slightly or not at all improved	253	402	462	469	231	349	393	366
	These 47 Patients' Averages	177	310	323	268	110	184	154	116
Partial Cooperation	15 Patients Tests improved	189	330	364	284	119	218	215	157
All	62 Patients Averages	180	315	339	272	112	192	169	126

But even if no assumptions about the outcome, had each patient cooperated fully, are made, the weight reduction of these 62 hyperglycemic patients still caused 57 per cent of them to dispose of glucose normally. Another 33 per cent showed improved ability to dispose of glucose. Only 10 per cent were not improved. Analysis of the results obtained with the 47 patients who cooperated fully showed that 77 per cent of them became able to dispose of glucose normally.

Twelve of the patients whose tolerances became normal avoided gain of weight, and the glucose tolerance tests were repeated 6 to 29 months after the first normal tests were obtained. Each of the last tests was normal also. Since these patients had been eating the usual mixed diet in the interval between the first and last normal test, the benefit from the reduction diets, which were necessarily restricted in carbohydrate as well as fat to lessen the caloric intake, cannot be attributed to the carbohydrate restriction.

DISCUSSION

Other writers who have dealt with the relationship between obesity and delayed utilization of glucose have taken it for granted that the patients were diabetic. By definition they would be suffering then from an hereditary incurable disease of the Islands of Langerhans that prevented them from forming normal amounts of insulin. We are contending that the delayed utilization of glucose encountered in obese adults is usually of a fundamentally different nature for these reasons. (1) The disturbance is mild, often so mild that it may exist for many years without causing symptoms even though it is not treated. Clinical acidosis does not occur. (2) Delayed utilization of glucose is a common accompaniment of obesity. Thus Kisch³ found that about 50 per cent of all markedly obese persons were glycosuric. Paullin and Sauls⁴ reported that 58 per cent of 26 obese persons who were aglycosuric gave abnormally high glucose tolerance curves. John⁵ performed glucose tolerance tests on 182 aglycosuric obese patients and found that 65 per cent of them were unable to dispose of ingested glucose at the normal rate. Ogilvie⁶ concluded that the impairment of tolerance was related to the duration, not the degree of obesity. It took more than 11 years of obesity to cause delayed disposal of glucose. On the other hand, every woman who had been obese more than 18 years, showed delayed utilization of glucose. These investigations indicate that prolonged obesity usually causes changes in the organism, one of whose manifestations is delayed utilization of carbohydrate. (3) Those who would still contend that these obese hyperglycemics are diabetic and that their inherent pancreatic weakness is accentuated by the obesity, would necessarily have to assume that the majority of persons are diabetic. Are they willing to do so? (4) If our patients are mild diabetics whose inherent weakness becomes clinically apparent when their total metabolism is increased by the obesity, then those whose inherent fault has become hidden again through reduction of weight

should manifest their diabetic state when they suffer from an infection. Since we have had only one opportunity to observe this condition, we can do no more than report that Mrs. S, whose glucose tolerance had become normal through reduction of weight, subsequently was admitted to the hospital one week after the onset of an upper respiratory infection of increasing severity. Her temperature on admission was 104° F, she had pain in the chest and was raising bloody sputum. Nevertheless, the urine was sugar free. (5) If the severity of diabetes is augmented by increasing the weight of the patient, it should be possible to demonstrate this effect in the juvenile diabetic. We have made this attempt. Miss B is a young woman who presents the classical picture of severe diabetes. When she weighed 101 pounds she was placed on a diet that contained 300 grams of carbohydrate and 2800 calories for five days, and she received no insulin. During the three last days the 24 hourly urinary glucose averaged 211 grams, and the glucose tolerance test performed the next morning was: fasting, 264, first hour, 484, second hour, 516, third hour, 432. Four months later when her weight had increased to 132 pounds, she was placed on the high carbohydrate diet again, without insulin. The 24 hourly excretion of glucose averaged 209 grams this time and the glucose tolerance test was 286, 444, 465, 500. A gain of 31 pounds did not lessen her ability to dispose of glucose.

It will be recalled that a few of our obese hyperglycemics were not improved by reduction of weight to normal. One explanation is that they are individuals who are victims of diabetes of the juvenile type. It is also conceivable that the prolonged hyperglycemia caused organic changes in the Islands of Langerhans, since Best⁷ has shown that high blood sugars do damage the insular cells in dogs.

During the year 1936, 370 new cases were classified as diabetic after thorough study. Three hundred and sixteen of them were 30 or more years old, and 57 per cent of these adults were obese on admission. Therefore, approximately one-half of these 370 patients, whose ages ranged from a few months to 71 years, were obese when they were admitted. Our experience has shown that adequate reduction of weight will abolish all evidence of lessened utilization of carbohydrate in at least 60 per cent of adult obese hyperglycemics. Since one-half of all the new cases classified as diabetic were obese, it is permissible to predict that thorough-going reduction of weight of the obese members of the group will abolish the retarded utilization of glucose in one third of the patients who are believed to be suffering from diabetes mellitus.

CONCLUSIONS

The glucose tolerance tests became normal in 77 per cent of those adult obese hyperglycemic patients who were willing to undergo adequate weight reduction. Reasons have been given to support the belief that these persons

have not inherited an incurable disease of the tissues that produce insulin
We explain the hyperglycemia as a manifestation of obesity

The normal or ideal weight of an adult human being cannot be stated with great precision. The figures compiled by the large life insurance companies are closest to the ideal for the present, even though the weight and height were obtained on clothed persons who had not removed their shoes and who were postprandial. Details may be obtained by consulting Fisk's book "Health Building and Life Extension," 1923, Macmillan Co., New York.

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THE CLINICAL SIGNIFICANCE AND TREATMENT OF PYURIA *

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THE physician of today, whatever may be the nature of his practice, must know something about progress in all fields of medicine. Much progress has been made in recent years in knowledge concerning infection in the urinary tract. It is appropriate, therefore, to discuss before internists some of the clinical phases of urinary infection and its treatment. I take it for granted that most patients who come to the internist have symptoms other than those referable to the urinary tract, and that pyuria, when present, is discovered in the course of routine urinalysis. If it were otherwise, the modern sophisticated patient probably would consult his neighborhood urologist first. It should be said at the outset, however, that urologists look with some doubt on those who intrude in their field but do not belong to the guild. But then, since pyuria is a complication which may be common to patients who consult specialists in any field, including that of the internist, urologists are glad to reveal the secrets underlying recognition and treatment of it, up to a certain point.

Once pus cells have been found in the voided urine, what is their clinical significance? To begin with, it should hardly be necessary to state that pus cells found in voided urine may not have originated in the urinary tract. In most cases pus cells found in the voided urine of a *female* patient are absent in the catheterized specimen of urine from the same patient. The finding should *invariably* be checked by catheterization. I have seen many patients referred for urologic investigation because of persistent pyuria who never would have been sent had they been catheterized. When catheterization is inadvisable or impossible, a satisfactory specimen of urine can be obtained by careful cleansing of the external portion of the urethra and by spreading the vulva while voiding. Pus cells in the voided specimen of urine of the male patient, on the other hand, are of definite significance, particularly if the two-glass test is used and if the urine in the second glass is found to contain pus. If, however, the pus cells are found largely in the first glass, infection in the urethra secondary to chronic prostatitis must be suspected. In fact, the presence of a variable number of pus cells in the urine of a male adult usually is caused by some form of what Keyes has called "prostatism."

Patients may be observed who complain of several things, among them frequent micturition. On examination of their urine no pus cells may be found. These patients offer a clinical problem, even to the urologist. Most of them are women in the fifth and sixth decades. In many cases the symp-

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toms are caused by a chronic cicatricial type of urethritis which may cause little or no pyuria. Bacteriuria occasionally is observed without pyuria, and can be the cause of vesical distress. Interstitial cystitis may be the cause of frequent micturition and dysuria with little or no pus in the urine. The patient may have been told that vesical irritation is caused by pressure of adjacent pelvic organs. The truth is that pressure by intrapelvic lesions seldom causes frequent urination or dysuria. Rarely, allergy may explain some instances of vesical irritation. In some cases no etiologic factor may be found, even after a careful search, and the symptoms can be explained only on a functional basis—the so-called irritable bladder. An organic lesion is present somewhere in the urinary tract in most cases, and a careful urologic examination is indicated.

Merely to report the presence of pus cells in the urine, however, is of little clinical value. It is of equal importance to know whether any bacteria are present and if they are, what kind. Rough identification of bacteria can be made by means of Gram's staining of the urinary sediment. This simple method can be employed easily by any laboratory technician, and should be made a part of routine urinalysis. Cultural methods may be indicated for further identification of bacteria, but for most clinical purposes they are unnecessary.

If there is any advance in medical science to which the urologists have contributed in recent years, it is an increase in the knowledge concerning those bacteria involved in infection of the urinary tract. Only a few years ago many urologists scarcely knew the difference between a bacillus and coccus when they saw them under the microscope. Today they glibly quote the names of every bacterium ever heard of, and are familiar with many of the cultural characteristics of bacteria. In order to treat urinary infection intelligently a working knowledge of its bacteriology is essential. It will not avail to dust off your old textbooks on bacteriology, since present knowledge of the subject has been greatly revised and it will be necessary to consult current literature to bring yourself to date.

It is well known that the bacteria most commonly found in infected urine are either the lowly colon bacillus or the more tenacious relatives of that organism, the *Aerobacter aerogenes* and the *Pseudomonas aeruginosa*. Some observers would like to link the origin of the colon bacillus with the adjacent intestinal colon. The contention is that colonic stasis is a factor, and that it permits the colon bacillus to permeate the urinary tract. This never has appealed to me as being logical. Constipation or colonic stasis seldom causes urinary infection, to my knowledge. If it were a common factor, sulfaguanidine should control bacillary infection in the urinary tract, but it has proved to be much less effective than any of the other sulfamido drugs.

Among other gram-negative organisms frequently observed in infected urine are included members of the genera *Proteus*, *Pseudomonas* and *Salmonella*. These organisms are urea-splitters and, as a result, the urine often becomes alkaline, with resulting deposition of calcium on the mucosal

mucosa of the bladder or in the kidney. These bacilli may be exceedingly difficult to eradicate, even with recently discovered chemotherapy. Among the gram-positive cocci, micrococci are most commonly observed. They usually are present in the urethra and are comparatively innocuous, although occasionally they may become virulent. Staphylococci are not commonly found in the urine but, when present, can be virulent formers of abscesses. Often they are associated with formation of calculi. Streptococci seldom are the active agents in urinary infection, except in the form of the *Streptococcus faecalis*. This bacterium usually is a secondary invader, after primary infection in the urinary tract, and usually is found in mixed infections. Unless its presence is detected, it may be the cause of persistent infection after the bacilli have been eliminated. Many patients with pyuria are observed in whom a careful search for bacteria, both by Gram's staining of the urinary sediment and by culture, reveals none. This may be difficult to explain, but bacteria may be present which are so few in number and have become so attenuated that it is difficult to discover them by the usual methods of investigation. The theory of amicrobic pyuria has been advanced, but it does not seem to have a logical basis. Some of these patients will respond to chemotherapy without the organisms being found.

The possibility of tuberculosis must be considered in every case of persistent pyuria unless it is proved not to be present. There has been a decided change in the clinical picture of patients with renal tuberculosis in the last decade or two. It is evident that a relative immunity to the disease has been developed in this country. The patient of 30 years ago complained of severe dysuria and urinary frequency, many pus cells were found in the urine and the diagnosis was made with comparative ease. Its clinical recognition today may be exceedingly difficult. The symptoms usually are slight, only a few pus cells may be found in the urine, and on cystoscopy the bladder may appear normal. The usual carbolfuchsin staining of the sedimented urine should be done coincident with Gram's staining. The presence of the *Escherichia coli* in the sediment should not lead one to exclude tuberculosis, however, since it may be coincident in the urine with the *Mycobacterium tuberculosis*. If there is anything suggestive of tuberculosis in the course of physical examination, or if pyuria is not eliminated by chemotherapy, the urine should be examined for the *Mycobacterium tuberculosis* and a more sensitive method of staining (with auramine) should be used. Experience with this new stain has shown that it will detect the presence of the *Mycobacterium tuberculosis* in the urinary sediment much more often than will carbolfuchsin stain. In case of doubt inoculation of guinea-pigs remains the most nearly accurate test, and should be employed. Cultural tests for tuberculosis, although satisfactory in the hands of some, do not have the accuracy of inoculation of guinea-pigs. Treatment of this type of tuberculosis can be summarized by regarding the lesion as unilateral from a surgical standpoint, and bilateral from its postoperative aspect. Postoperative medical supervision is of primary importance in the postoperative

result. Chemotherapy is of no value unless there is a secondary bacillary or coccic infection in the bladder. When pyuria persists after nephrectomy, this possibility should be considered.

Although patients usually come to the internist primarily because of lesions in various organs other than the genitourinary tract, not infrequently their condition is complicated by the presence of a variable degree of urinary infection. In the surgical field pyuria probably is most often observed in the presence of lesions in the gall-bladder, the thyroid gland, the gastrointestinal tract and the pelvic organs. The questions usually asked by my colleagues in clinical diagnosis are (1) What is the source of the pyuria? (2) Can its treatment be delayed until the major lesion is taken care of? and (3) Will the urinary infection interfere with surgical treatment of the primary lesion, if operation is indicated?

At the clinic it has been our experience that urinary infection seldom interferes with surgical treatment unless symptoms are present which indicate acute or severe lesions in the urinary tract. Provided renal function is normal, the existence of mild chronic pyelonephritis or cystitis seldom causes difficulty after operations for lesions in other organs. It would hardly be advisable, however, to proceed with surgical treatment of the primary lesion without knowledge of at least something about the source of the pyuria. It should be determined whether or not urinary obstruction exists or whether there is a renal lesion which might seriously interfere with operation. Occasionally, the lesion in the urinary tract may require treatment before therapy can be directed to the patient's major condition.

Probably the more common medical conditions with which pyuria may be associated are diabetes and circulatory lesions. Urinary infection formerly was a rather frequent complication of diabetes but, since the advent of insulin, it is observed much less frequently in such association. When pyuria is present in such a case it usually is caused by mild bilateral pyelonephritis and cystitis. Unless some underlying lesion is present in the urinary tract, this type of pyuria should respond to intelligently conducted chemotherapy, although in some cases of diabetes the infection is unusually resistant. Occasionally, a few pus cells are found in the urine in cases of glomerulonephritis, and the presence of a complicating or etiologic infectious element may be inferred. In fact, in some cases in which a variable number of pus cells are present in the urine it may be difficult to determine whether or not the nephritis is primarily of infectious origin. In such cases it would be desirable to search for bacteria and to visualize the urinary tract in the excretory urogram for evidence of deformity in the renal pelvis or calices. In the treatment of these patients the presence of possible foci of infection should be carefully determined, and, if foci are found, they should, of course, be eliminated.

It should be unnecessary to say that in every case of urinary infection without apparent cause a careful search should be made for foci of infection. This search should include roentgenograms of teeth, examination of tonsils,

for hidden crypts, and evidence of infection in the prostate gland, or the cervix and vagina. Incidentally, it should be remembered that tonsils or teeth may infect the prostate gland, which in turn may be the immediate source of cystitis or of ascending pyelonephritis. The removal of such foci may be far more efficacious in overcoming infection than chemotherapy. It would seem logical to suppose that chronic infection in any organ might act as a focus for infection in the urinary tract. Clinical experience, however, does not definitely corroborate this. However, acute infections involving various organs not infrequently are complicated by infection in the urinary tract. I have observed many patients with urinary infection coincident with acute or subacute cholecystitis in whom the urinary infection disappeared after removal of the infected gall-bladder. On the other hand, the incidence of cholecystitis among patients who have chronic pyelonephritis is no greater than the average.

A question often discussed is, what is the significance of pyuria in cases of hypertension? In view of the general acceptance of the theory that a unilateral renal lesion can be an etiologic factor in hypertension, this question assumes major importance. It has been my experience that there are very few patients suffering from hypertension resulting from a unilateral renal lesion who have no pus cells in the urine, or a history of previous urinary infection. It is true that some patients with atrophic pyelonephritis have very few pus cells and that the urinary symptoms of such patients may be obscure. It is evident that in every case of hypertension with pyuria thorough study should be made of the urinary tract. Unfortunately, the percentage of patients suffering from hypertension with unilateral renal lesions is limited, and the percentage of those who are permanently relieved by nephrectomy is even more limited. Nevertheless, the occasional patient who is cured by nephrectomy makes intensive search for this particular condition worth while. Although at the Mayo Clinic we do not make routine urographic studies for every patient who has hypertension, it is advisable to do so for all patients who have urinary infection or have had it, and also for those who previously have undergone a renal operation. Why renal infection is only occasionally an etiologic factor in hypertension probably was best explained by Page, who stated that renal pathology such as that resulting from infection is of importance only if the intrarenal pulse pressure is disturbed.

Having determined that the pyuria persists in the catheterized specimen of the female patient or in the voided second glass in the male patient, and having carried out simple Gram's staining of the urinary sediment in order to get a rough estimate of the bacteria present, and having excluded an obstructing or infected prostate gland as the source, what next should the internist do? It is our custom at the clinic to make a plain roentgenogram of the urinary tract of every patient who has pyuria or a history of pyuria, irrespective of symptoms. This procedure should be more widely available and should be employed in routine diagnosis. Many clinicians seem to think

that a urinary calculus could hardly be present without a history of pain. It is surprising how often so-called silent or symptomless stones in the kidney, ureter, bladder or prostate gland are present, discovered in cases in which pyuria is the only clinical clue. There is nothing more embarrassing than to have the patient you treated unsuccessfully for pyuria consult another physician who finds urinary calculi. When shadows are found in the renal roentgenogram it should be remembered that calcified areas caused by renal tuberculosis also may cause shadows, which usually are recognizable in the roentgenogram.

The internist might also be justified in going a step farther by making an excretory urogram. This is a comparatively simple procedure, which often reveals lesions in the urinary tract that are least suspected. Although it may require wide experience correctly to interpret some of the excretory urograms, in many cases the nature of the lesion when visualized can be recognized by the inexperienced practitioner. The value of excretory urography is not sufficiently appreciated by the average physician, it should be more generally employed in differential diagnosis. Not alone can it identify a renal shadow found in the plain roentgenogram, but it can reveal hydro-nephrosis and other lesions which are not suspected on the basis of the symptoms.

Having satisfied himself by these various means that the infection is an uncomplicated one, what is the internist's next procedure? The average physician of today probably would not hesitate to employ one of the sulfamido preparations against uncomplicated urinary infection and, in many cases, he would be rewarded by elimination of the pyuria after such therapy. What form of chemotherapy is it best to employ against urinary infection? As a general rule it is advisable, as far as possible, to use the drug which fits the bacteria present. If gram-negative bacilli are present, the choice lies between sulfamido drugs and preparations of mandelic acid. There is still a difference of opinion as to which drug is preferable. Most bacilli do not like an acid medium. In many cases of uncomplicated bacillary infection a combination of ammonium chloride or nitrate with mandelic acid, which lowers the hydrogen ion concentration of the urine to 5.3 or less, will eliminate the infection in six or eight days. This drug is even more efficacious than sulfamido drugs in combating infection caused by the *Streptococcus faecalis*. The *Proteus vulgaris* may offer difficulties if the hydrogen ion concentration of the urine cannot be reduced by means of acidification. In fact, when the urine remains very alkaline no form of chemotherapy may avail. Unfortunately, patients of advanced years or those who have reduced renal function do not tolerate preparations of mandelic acid well. It is also true that some patients cannot tolerate sulfamido drugs, and for many of these the mandelic preparations will serve admirably. It must be said, however, that it is truly astounding to observe how bacillary infection will be eliminated by means of the sulfamido drugs. Against coarct infections

preparations of mandelic acid are of no value and when they are present the sulfamido group of drugs is preferable

What particular sulfamido drug is most efficacious in the treatment of urinary infection? The list from which a choice can be made is truly imposing. It would seem, on the basis of experience, that those drugs most recently proposed, namely, sulfathiazole and sulfadiazine, have the advantage of causing fewer toxic reactions than do others and of possessing low acetylation and rapid excretion. There are those who prefer the sodium sulfa preparations. Sulfacetimide is another recent sulfamido drug which is extolled by some. Sulfaguanidine, which can be administered in the largest dosages without causing subjective reactions, is less effective than the others, although occasionally it is very bactericidal. There are several others, in fact, it might be claimed that this list is not up-to-date. It is hardly necessary to warn you against the danger of a patient's idiosyncrasy and variability in reaction to sulfamido drugs. It should be remembered also that if the infection does not respond to one sulfamido drug, another should be used. I have often observed that urinary infection which was resistant to one form of sulfamido drugs rapidly disappeared when another sulfamido drug or a preparation of mandelic acid was tried. Another observation should be made: it is seldom that sulfamido drugs interfere with the coincident administration of other drugs.

The subject of the dosage of the sulfamido drugs now arises. The internist is accustomed to dealing in large figures in the employment of sulfamido drugs, and he might look askance at the economical dosage employed by urologists. Experience has shown that an initial daily dosage of 3 or 4 gm. is all that is necessary against most uncomplicated infections in the urinary tract. In fact, the effective dosage is gradually being reduced and in most cases an initial two-day dosage of 3 gm. is being replaced by one of 2 gm., administered for a period of six or eight days. When such a low dosage is employed severe reactions to sulfamido drugs described by those who employ them in treating profound systemic infections are seldom seen. Urologists have the advantage that the infected field is immersed in sulfamide-bearing fluid, as is also the surrounding zone of reaction in the tissues, although the latter is the predominating factor. In contrast to the procedure in the treatment of systemic infection with a sulfamido drug, it seldom is necessary to determine the concentration of the drug in the blood in treating urinary infection, since this concentration is low and does not exert much influence so far as results are concerned.

Although this may not be the place in which to discuss toxic reactions in the use of sulfamido drugs, there is one complication not infrequently observed which deserves consideration and that is anuria developing as the result of acetylation and the deposition of crystals in the renal tubules. Although there is a difference in the degree of acetylation caused by the various sulfamido drugs, they all may be guilty of renal blockage. The degree of subjective toxic reaction which results is no criterion. The drug which

causes the least symptomatic reaction is one of the worst offenders in this respect. I refer to sulfadiazine. Sulfadiazine should not be regarded as being entirely innocuous, in spite of what Paul de Kruif has written in the *Reader's Digest*. Only the other day a report came from Bellevue Hospital in which it was disclosed that 10 patients had anuria after the use of sulfadiazine, with two deaths, in spite of treatment. One of these two deaths occurred after the administration of only 12 gm of the drug in four days, or a dosage of 3 gm daily. It should be emphasized that anuria associated with the use of sulfadiazine demands the immediate cooperation of the urologist. By the introduction of ureteral catheters and lavage of the ureters and the renal pelves, the blockage usually can be relieved. It is obviously advisable to start such treatment in the early stages of anuria. Crystallization otherwise may become so dense that lavage is futile and injury to the renal cells may be fatal.

In case pyuria persists in spite of a thorough trial of chemotherapy, what are the possible causes of failure of such therapy? A common cause is inadequate and incorrectly selected chemotherapy. This usually is the result of (1) failure to identify the bacteria present, (2) failure to recognize the existence of a mixed infection, (3) failure to select the correct drug for the particular bacteria involved, and (4) the occurrence of a toxic reaction. Probably the most important factor in the failure of chemotherapy is the existence of a primary lesion in the urinary tract which is the cause of pyuria; if such a lesion is not eliminated, chemotherapy of course is worthless. The list of such lesions is long, and even a brief discussion of them would lead far afield. Among them, however, those most commonly observed are chronic pyelonephritis with diffuse cicatricial changes in the renal tissues, inadequate drainage involving either the renal pelvis or the bladder, urinary calculi and tuberculosis. Needless to say, recognition and treatment of these lesions demand the knowledge and skill of the urologist. It is here that the urologic west begins, so to speak, with its wide horizons and unlimited possibilities, and it is here that my discussion will cease.

SUMMARY

In summary these data may be repeated. Pus cells found in the voided urine of the female patient are of little or no clinical significance. In such instances a specimen of urine obtained by catheter is necessary. Pus cells in the voided urine of the male patient are of greater clinical value, and particularly if the two-glass test is employed. It is of equal clinical importance to determine the presence and kind of bacteria in the urine. Intelligent treatment of pyuria is dependent on a knowledge of its bacteriologic aspects. Rough identification of the type of organisms present is possible by the simple method of Gram's staining of the urinary sediment.

Bacillary infection is observed in most cases. The colon bacilli or the *Aerobacter aerogenes* are the organisms usually found. Mixed infections

may be present most often it is caused by colon bacilli with *Streptococcus faecalis*. Unless this fact is recognized, chemotherapy may fail. Renal tuberculosis is a frequent cause of pyuria which resists chemotherapy. In recent years the symptoms and severity of the infection caused by renal tuberculosis have become milder and the recognition of such tuberculosis often is difficult. Auramine as a stain for the *Mycobacterium tuberculosis* is of greater value than carbolfuchsin.

Pyuria may be coincident with lesions situated in other organs. Acute cholecystitis coincident with pyuria often is observed. When a lesion requiring surgical attention is present, the question might arise, would urinary infection interfere with operation? As a rule it does not, but a search should be made for the cause of the pyuria. A careful search for foci of infection and the removal of them is always necessary. Pyuria or a history of previous urinary infection occurring with hypertension should be the guide to complete urologic investigation. In the presence of pyuria important clinical data can be obtained by such simple tests as the making of roentgenograms and excretory urograms.

Intelligent chemotherapy depends on identification of the bacteria. In cases in which the situation is complicated, infection caused by the *Escherichia coli* often responds to treatment with mandelic acid. Of the sulfonamides, sulfathiazole and sulfadiazine probably are preferable. The danger of acetylation with the deposition of crystals and the occurrence of anuria must be considered. Immediate catheterization of the ureters and pelvic lavage are indicated.

Persistent pyuria in spite of chemotherapy usually is caused by some underlying pathologic lesion in the urinary tract which requires careful examination and treatment by the urologist.

A HIGH FLUID INTAKE IN THE MANAGEMENT OF EDEMA, ESPECIALLY CARDIAC EDEMA

I THE DETAILS AND BASIS OF THE RÉGIME

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THIS paper presents the details of a régime which, in the past eight years, has been used in approximately 600 separate periods of treatment carried out on a series of about 400 cases of advanced disease, 96 per cent of which were cases of cardiovascular-renal disease. In this series there were about 375 cases, or 94 per cent, with gross heart disease, of which over 200 showed gross edema.

Only a few of the reasons which led to a trial of this régime can be mentioned here. There are clinical observations^{77 to 93} from Withering through Austin Flint to recent times which are not discouraging to such a trial, and many facts are to be found in clinical investigations^{23 to 70} of the last 15 years which appear not only to weaken the force of the usual objections to a high fluid régime, but also to explain the paradox of its good results. The 50 year old practice of the restriction of fluids in edema⁸⁷ appears incompatible with principles derived from renal-function and water-balance studies^{1 to 11}.

The chief reasons urging a trial of this régime, however, were found in personal observations † at the bedside, such as

- 1 The unmistakable clinical signs and symptoms of severe dehydration in some cardiac patients with massive anasarca

- 2 The toleration by enlarged and fibrillating hearts in thyrotoxicosis of large amounts of water by mouth and by vein before and after operation

- 3 Recoveries from so-called "postoperative nephritis," with correction of anuria and clearing of edema, by the administration of 6,000 to 7,000 c c of water for several days, mainly isotonic solution by vein

- 4 The clearing of massive edema without disaster in cases of advanced nephritis, which often showed choked discs or grossly diseased hearts, in the face of intakes averaging more than 4,000 c c daily

GENERAL CONSIDERATIONS

The fundamental thesis on which the régime is based was quaintly expressed by Baynard⁷⁷ in 1722: "salts creep with the chyle into the blood and have no way out but by the urine." A painstaking correlation of facts found in the newer investigative studies of body fluids^{24 to 26}, renal function,^{1 to 11} and body-water-exchange^{27 to 30} appears to clinch the

the discrepancies in the old idea that "salt retention" is the *primary* factor in the formation of edema. Changes in venous pressure^{52, 53, 54} and especially plasma proteins⁴⁸ follow as often as they precede the development or clearing of edema. Starling,²² himself, emphasized the probable *primary* rôle of salt retention in some forms of edema.

Regardless of how the edema is formed,^{38 to 54} it appears reasonably well established that

1 Edema fluid is a simple volume increase of the interstitial fluid. It can accumulate and exist only if its materials have been supplied and retained. For each two pounds of edema these materials consist of about 10 grams of an alkaline mixture of sodium salts (about 5 parts sodium chloride with 1 part sodium bicarbonate, yielding a pH of 7.4) and 1,000 c.c. of water as solvent for the salts^{26, 34, 35, 36, 37}. The increased volume of interstitial fluid is subject to the same vicissitudes as the normal volume, thus chloride or sodium deficits may exist, or water alone may be given up for vaporization and the whole mass of "brine" become concentrated and a true cellular dehydration exist. True dehydration in these "brine-logged" patients is, therefore, no real paradox.²¹

2 The alkaline edema fluid remains inertly and indefinitely retained or "stored" in the internal environment unless the bicarbonate fraction of its sodium salts is used up by the ever-forming metabolic acids^{35, 37} or by ingested acids. Acidification incites the kidneys to balance the threat to the hydrogen-ion concentration of the body fluids by elimination of neutral or acid sodium salts or, as often expressed, "acidification mobilizes the sodium"^{3, 8}. As the *sodium* leaves the body via the kidneys its *water of solution* is free either (1) to leave the body as urine water, giving weight loss with diuresis, or (2) to leave the body as water vapor, giving weight loss with no diuresis, or (3) to remain within the body to remedy body fluid concentration and cell dehydration, giving, by a shift of water to the cells^{23, 24} a disappearance of edema with no weight loss and no diuresis.

The retention of alkaline and the elimination of acid salts is a physiologic process^{35, 37} which keeps the internal environment constant in volume as well as composition. To maintain acid base equilibrium slight changes in volume of interstitial fluid occur constantly throughout the 24 hours. If continued indefinitely in the one direction a continuous augmentation of volume of interstitial fluid leads eventually to clinical edema. In the other direction, in the absence of adequate water for the regulatory function of the kidneys, the continuous elimination of salts at the expense of body water leads to cellular dehydration and body fluid concentration and, finally, when about 8 per cent of the body water is exhausted, to anuria, accumulation of acid salts, and acidosis.

3 The sodium leaves the body via the kidneys in solution as urine, water reaches the kidneys only after all other demands of the body for water are met^{6, 11}, the amount of urine-water needed for the elimination of the so-

dium depends upon the functional capacity of the kidneys.⁵ Therefore, sufficient water must be supplied to the body so that *enough* water will reach the kidneys for the elimination of the sodium. The kidneys as "ultimate guardians of the internal environment"³⁵ are capable, even when intrinsically diseased or their function extrinsically impaired, of regulating the volume and composition of the internal environment if they receive enough water.^{5, 6} Thus they prevent acidosis by eliminating neutral or acid sodium salts if an excess of sodium is present, or if sodium is at a premium they discriminate, conserve sodium, and prevent acidosis by eliminating other salts.^{71, 73, 77} They fail partially or completely in their rôle of guardian when an inadequate amount of water is available for their use.^{5, 15}

It follows from the above that the aim of this régime is to:

- 1 Decrease the ingestion of the material essential to the formation of edema and to encourage the mobilization of sodium already retained, by giving a diet restricted in sodium and yielding a neutral or acid ash
- 2 Increase and hasten the normal effect of the metabolic acids, by the administration of minimal amounts of acid drugs
- 3 Facilitate elimination of the mobilized sodium via the kidneys and avoid the development of true cellular dehydration, by administering plain water in adequate amounts, i e., adequate according to water balance principles.^{6, 13}

The trial of a régime based on these considerations was begun in the fall of 1933. It soon became apparent that the régime permitted the administration of large amounts of water to very ill edematous patients with impunity and benefit and with results better than those obtained previously by restricting fluids, whether the primary disease was nephritis, cardiac disease, eclampsia,^{75, 76} pernicious anemia, or some "idiopathic" syndrome.*

DETAILS OF THE RÉGIME

Eight years of experience have disclosed many points which have improved results and shown that good results depend on the care with which the following details are enforced. It is not sufficient and is often productive of disappointing results to write as orders, for example, merely "Force fluids, low sodium diet."

Acid and Other Diuretic Medication Strictly speaking, these are not needed in the régime. The physiologic process of metabolism yields sufficient acid to use up slowly the bicarbonate fraction of the stored sodium mixture and incite its elimination if adequate water is furnished and the ingestion of an excess of alkaline ash is stopped. Usually slowly, but often with surprising rapidity, edema disappears with simply the neutral diet and

Practically, however, acid drugs are often used to speed the elimination of edema for psychological and economic reasons as well as reasons of comfort. They have the added practical advantage in both hospital and home management of protecting from errors or lapses in the diet.

We use only dilute hydrochloric acid or ammonium chloride because their ions are entirely familiar to the body. Theoretically, a pure acid should be most effective. We have found well diluted hydrochloric acid to be so, regardless of its presence or absence in the gastric secretions. It is obvious that large amounts of ammonium chloride unnecessarily increase the total solids which must be eliminated.

Mercurial diuretics are used infrequently to speed elimination when the degree of the edema is a major cause of discomfort. In only the most advanced and resistant cases is their use necessary in this régime. When they are used the water given is increased⁵¹ to a maximum to avoid the post-diuretic dehydration and shock so often noted with restricted fluid regimens^{55, 56, 57, 58}.

High protein diets,⁹ acacia,^{59, 60} thyroid extract, and vitamin B have not been used in order not to confuse results and to limit variables as much as possible.

Hypertonic solutions are not used^{62, 63}. In our experience *no case* resistant to this régime (because of our inability to administer sufficient water to make it effective) has responded satisfactorily for any length of time to hypertonic solutions and restriction of fluids.

Administration of Acid Drugs When no oral intake is possible we content ourselves with supplying water parenterally and depend on the constantly forming acids of metabolism to mobilize sodium. If response is slow, 1–2 c c of mercurpurin is given after a day of good intake and the total intake increased afterwards to protect from post-diuretic dehydration.

If the patient is only able to take clear liquids, a few drops (2 to 5) of diluted hydrochloric acid in each glassful is often well tolerated and often serves to speed elimination.

When the oral intake is well established or the initial neutral diet is tolerated, 5 to 10 drops of diluted hydrochloric acid may be given in a full glass of water every hour from 7 00 a m to 7 00 p m, or it may be given 15 to 30 drops at each meal or feeding.

Ammonium chloride is given for reasons of convenience or if the acid is not tolerated, rarely in a greater amount than 15 grains four times daily (4 grains daily), and usually not more than 2 or 3 grains daily.

After dismissal only the more severe cases, or milder cases who neglect the diet grossly, need the acid medication. These rarely need more than 45 grains (3 grains) of ammonium chloride or 40 min (2 to 3 c c) of diluted hydrochloric acid in the day.

Dietary Regulation of Sodium Meticulous attention to diet is not necessary or logical if edema is mild and has no tendency to recur. However

when massive edema is resistant to treatment or continually recurs, diet therapy is rewarded as richly as in cases of severe diabetes

Too frequently we consider obstinate cases as terminal or not subject to further improvement because they respond no longer to frequent and heavy doses of mercury and acidifying drugs and strong hypertonic solutions. Many such cases will respond and remain evenly edema free on a neutral diet. All cases are easier to manage and require less mercury and acid. The diet in our experience is no more difficult to explain or to enforce than a diabetic or ulcer diet. Even the recalcitrant patient soon comes to prefer it to the disability and suffering of his edema and the expense and inconvenience of intravenous mercury and hospitalization.

The diet is not simply a low salt diet, nor is it merely a low sodium diet. At all times it must yield a neutral or slightly acid ash. This prevents the neutralization of the metabolic acids which mobilize already stored sodium, and prevents the retention or "storage" of what sodium is taken in the diet. Some of Schroeder's⁹³ cases show that edema does not clear on a diet in which salt is reduced to the very low figure of 0.5 gram, a figure at which the *reaction* is basic.

Construction of a diet to fulfill these requirements depends simply on our knowledge⁹ that milk, all vegetables, and all fruits (except prunes, plums, and cranberries) yield an excess of alkaline ash. We must, therefore, not only restrict table salt and sodium salts but must insure the balancing, at each feeding, of the foods mentioned above with the foods that yield an excess of acid ash, which are meat, chicken, fish, eggs, cereal foods (including corn) and the three excepted fruits mentioned above. (Appendix "Skeleton Outlines")

The familiar Karrell diet, at the point where eggs, cereal and toast are added, if low in salt, can be just such a diet. In a patient strong enough to take food, starting such a diet is often followed by a prompt diuresis and loss of edema. This is not simply the result of sodium restriction and the supplying of acid; the non-liquid articles of the diet supply 700 to 1,200 cc of water for the use of the body.⁹⁴ A very ill patient who voluntarily drops to such a diet, or who works up to it, may lose edema quickly and be considered to have had a "spontaneous diuresis." The effectiveness of a high protein diet or a "dry" diet may well be due to the fact that such diets almost of necessity yield a marked excess of acid ash.

Either in hospital or at home one must guard against the ingestion of anything which renders useless the restriction of sodium or unbalances the acid-base proportion. A few glasses of milk or citrus fruit juice from the between-meal nourishment tray or a few doses of sodium bicarbonate for "gas" or indigestion may result in failure of the regime. Extra alkaline fruit juice or milk can be fairly well balanced by about 15 drops of the cup or diluted hydrochloric acid. If the primary disease requires the use of the sulfonamides or salicylates, it is essential to prescribe calcium carbonate to go with them instead of sodium bicarbonate, and to use active charcoal

acid instead of sodium salicylate. Patients must be warned against commercial salt substitutes (mainly sodium salts of some acid), against "soda" and commercial alkalis for indigestion, and against forcing fluids with unlimited amounts of milk or alkaline fruit juices. Conversely, acid-base proportion may be unbalanced by failure of the patient to eat the acid-ash foods offered him in any one feeding. Every item of each meal or feeding should be eaten, but if anorexia or caprice results in the omission of acid-ash items, equivalent basic-ash items must be omitted. (See Appendix "Precautions for Neutral Diets")

The Diets The diets used in the régime are based on the "neutral" diets and on the tables in Newburgh and MacKinnon's * *Practice of Dietetics* ⁸

The "Initial Neutral Diet" is appropriate as soon as soft food is tolerated. It yields only about 0.85 gram of sodium and an excess of acid ash amounting to about 100 cc of tenth normal hydrochloric acid. It is usually the first diet ordered in the hospital and it is very effective for home use when hospitalization has been refused or in the event of a minor recurrence of edema after discharge. (Appendix "Initial Neutral Diet")

As the ability to take food increases the Newburgh-MacKinnon tables permit the construction of liberal "full" neutral diets to fit any caloric requirement and any coincident disease such as diabetes or peptic ulcer or obesity. (Appendix "Full Neutral Reduction Diet")

At the time of discharge, if it appears that the neutral diet tables are likely to prove too difficult, a quite effective, simplified diet may be furnished. Strongly alkaline vegetables and fruits are forbidden entirely, milk, vegetables and fruits, with the exception of prunes, plums and cranberries, are specifically limited in amounts to insure a definite preponderance of acid ash. (Appendix "Full Neutral Diet")

After edema is gone and if for psychological reasons anorexia develops on account of the tastelessness of the food, a minimum of salt in the cooking combined with an increase in the acid ash of the diet will often be tolerated without recurrence of edema, within limits, *reaction* is more important than total sodium.

These diets are rich in milk, eggs, and fresh meat, and liver, yeast and wheat germ may be given in any amount. But if iron or vitamin deficiency is present or is feared, especially during the short period of the "initial" neutral diet, vitamin and iron supplements may be given.

The High Water Intake In some moderately severe cases attention to the primary disease, the use of acids, and the regulation of sodium ingestion may either separately or in combination so lessen the body's needs for water that elimination of the edema occurs in spite of a restricted intake. However, even in these cases the liberal use of water does away with discomfort from thirst, makes the work of the kidneys easier and protects the cells from any degree of dehydration.

* Frances MacKinnon gave us helpful criticism of the Appendix diet lists.

In the most severe cases, however, very large amounts of water may be needed for water vapor and for urine water. Unless enough water is administered edema either does not clear at all; or it clears in part or even entirely but only at the cost of a degree of concentration of body fluids and of dehydration of the cells more harmful to the cells than the presence of edema.^{55, 56, 57, 58, 59, 60, 61, 62, 63} In such cases, until advancing disease makes it no longer merciful or possible to administer large amounts of water, edema can be cleared, its recurrence prevented, and dehydration avoided only by an adequate increase in the amount of water administered.

Much of the satisfaction with the almost universal practice of severe restriction of fluids⁸⁷ appears to be due to the protection from disastrous cellular dehydration during the early days of edema loss by the release of edema water for vaporization purposes, the salts being eliminated in a fraction of the water which held them in solution in the body. Later, as the edema water is exhausted, protection from otherwise inevitable dehydration⁸⁷ is afforded by relaxation of the water restriction or by increased amounts of diet water derived from increasing ingestion of food.

The Amount and Kind of Water Only renal-function and water-balance studies show us *how much* water is enough. In health about 1,200 c c are required for water of vaporization and stool, and 1,500 c c for a good margin of urinary water. In milder cases of edema we give a total of 2,500 to 3,000 c c of water as a minimum, leaving the water derived from the non-liquid portion of the diet (700 to 1,200 c c) as a safe margin.

Under certain circumstances, in severe illness, the needs of the body for water are greatly increased. Temperature regulation may use as water vapor 2,000 to 5,000 c c daily.¹⁴ Badly impaired kidneys may require 2,000 c c or more daily to eliminate 40 grams of solids,⁵ and when the maximum specific gravity is low we increase the intake by 1,000 to 2,000 c c over the usual amount. Dehydration may have resulted in a loss of body water, not electrolyte, that amounts to from 6 to 8 per cent of the body weight^{11, 12}; such a water deficit, of from 4,500 to 6,000 c c, must often be made up during the first few days before any useful amount of water reaches the kidneys.¹¹ Thus, a badly dehydrated, edematous patient with badly impaired kidneys and with a fever or much sweating, might require 8,000 to 10,000 c c of water for a day or two, and 4,000 to 5,000 c c daily thereafter.^{6, 12, 13}

Less than enough water for the needs of the body leads eventually to dehydration. *Any reasonable amount more than enough* does no harm because plain, unloaded water passes out via the kidneys¹⁴ rapidly and easily even when their function is badly impaired. Within a wide degree therefore, as Austin Flint¹¹ said, *more than enough* water is not too much. We have never encountered "water-intoxication" and suspect that these syndromes are due to disturbances of the electrolyte pattern.^{15, 16}

The best kind of fluid to use is indicated by Baynard (1722) who says, *that water is the best, which is most simple as having least content*.

Water is needed, not the solid content of fluids. Oral fluids should not carry large amounts of alkaline ash or salt, as do citrus fruit juices and salted broth. Parenteral fluids should carry no salt and a minimum of solute.

No normal saline is given unless the plasma chlorides are very low or there are marked clinical signs of hypochloremia or unless the carbon dioxide combining power is very low.¹⁰ We have repeatedly observed that when enough water is reaching the kidneys they are capable of conserving enough of the excess sodium or chloride of the edema fluid to rectify the electrolyte pattern, even while the water of the edema fluid is being rapidly eliminated.

Isotonic dextrose, 5 per cent in distilled water, is used because most of the solute is oxidized or stored in the cells. It is *the solution* which yields a maximum of plain water for the use of the body. In two instances we observed no untoward effects from the accidental administration of 1,000 c c of plain distilled water in about an hour. We commonly rehydrate our patients with diabetic coma with two-thirds normal solution.

Administration of Water It requires patience and some ingenuity to administer large amounts of water to the very ill. When nausea and vomiting or stupor are present, or for other reasons an adequate amount of water cannot be given orally, enough intravenous solution is given to bring the total intake up to the estimated desirable amount. Rectal administration of water is satisfactory only in the first few hours when general dehydration is marked, expelled enemas upset intake figures and may result in abnormal electrolyte losses.

Since the first trials of 300 to 500 c c of 10 per cent dextrose in 1933 the amounts administered have been increased. At present 500 c c or 1,000 c c of 5 per cent dextrose in distilled water are given from one to six times a day. On occasion 1,500 to 2,000 c c have been given continuously, without untoward effects, in from 60 to 100 minutes.

The only untoward reaction encountered (in only 20 of about 2,000 administrations) with the use of isotonic solutions that carry no diuretic, which justifies stopping the intravenous injections, was an increasing "sense of fullness", the symptom appears related to effects of the electrolyte of the solution rather than to its rate or volume. We suspect that many of the reported reactions are post-hoc affairs, episodes of the disease under treatment occurring naturally, or precipitated by fatigue and annoyance from slow-rate venoclyses.^{29, 30, 31, 33}

The most desperately ill cases have almost invariably shown evidences of severe dehydration associated with their massive edema.^{88, 89, 90, 91} The water of the first few intravenous injections is used to bring all of the body fluids up to a normal dilution and to relieve the water deficit of the cells.¹¹ During this period there is, quite naturally, often no diuresis, some gain in weight, and sometimes a visible increase in the edema. Coincidentally, there is usually such marked clinical improvement as to encourage one to persist. Persistence is usually rewarded, often in some very unpromising cases, by a diuresis and the clearing of edema.

When the oral route becomes possible, a tedious insistence is often necessary to bring the oral intake up to the point where it is wise to discontinue intravenous supplements. If the intake is poor on account of continuous semistupor, Austin Flint's practice³² of administering small amounts of water frequently through the night as well as through the day may be effective. When liquids can, at last, be taken freely it is important to recall the necessity of avoiding large amounts of alkaline-ash fruit juices, salted broth and milk.

As general improvement continues it is usually surprisingly easy to keep the intake at any level desired. Not infrequently, however, one encounters the patient whose oral intake is inadequate simply because of forgetfulness, obstinacy, or a life-long aversion to water. We have found it very effective to prescribe something in "homeopathic" doses to be taken in a glass of water every hour, or even every half-hour, from morning until about six at night. We use a few drops of hydrochloric acid, peppermint water, or a half a teaspoonful of wine (vide Galen's wine water³³).

Such efforts to increase oral intake so that intravenous supplements may be stopped are justified because all patients "do better" on an oral intake with even scanty liquid nourishment.

COMMENT

In any trial of the régime the details and precautions outlined above should be strictly followed. It would be wise to proceed at first as we did, making the trial on quite mild cases or on cases that have obviously failed to respond to accepted régimes, especially until the dietitians and nursing staff are reasonably familiar with the régime. (Appendix, "Sample Hospital Orders")

Because we undertook these observations as a practical clinical investigation we often carried our intakes higher than optimum. As a consequence, we have repeatedly observed the rapid clearing of massive edema in the face of intakes averaging 6,000 or 7,000 or even 8,000 cc daily, in spite of the presence in some instances of pulmonary edema, choked discs, or convulsions at the time of admission.

In our hands this régime has proved effective in eliminating edema and preventing its recurrence in the most resistant type of case II, and so long as, it has been possible to administer adequate amounts of water. The type

* These phenomena appear to bear no direct relationship to anasarca and occur frequently in its absence. Pulmonary edema, for example, appears to be most directly related to an injury of the cells of the capillaries by a lack of oxygen or by a lack of red water. The "brinelogged" patient may need plain water to relieve anasarca which is not

of terminal case which has not responded to this régime does not respond to the usual régimes which restrict fluids and use strong hypertonic solutions or acacia. On the other hand, many cases of massive edema which had resisted well carried-out restricted fluid régimes have been observed to respond to this high fluid régime.

SUMMARY

1 A régime is presented which permits the effective management of edema with a high fluid intake by the proper regulation of sodium ingestion.

2 The régime is based on renal-function and water-balance principles which the accepted practice of the restriction of fluids appears to ignore.

3 The reasons for a trial of the régime are briefly indicated.

4 The details of the régime, some diet lists, and certain precautions are presented as they were evolved from eight years' experience with 626 separate periods of treatment of 402 cases.

APPENDIX

DIETS AND ORDERS

Skeleton Outline for Neutral Diets *

General Diet

Limited 24 hr Maximum	Basic-Ash Foods	vs Acid-Ash Foods	No Limit 24 hr Minimum
1 Pint	Milk	Eggs	2
2 Servings	Vegetables	Meat, fish, fowl	1 Serving
2 Servings	Fruits	Bread or cereals	5 Slices or servings
	except	Prune, plum, cranberry	as desired

Initial Diet

6 Cups	Six small feedings		One item per cup
6 Servings	Milk or	Egg or	1
	Milk and	Bread or	2 Slices
	Cream (1/3)	Cereal	1 Cup

Precautions

- 1 No salt or soda in or on food.
- 2 No prepared foods containing salt.
- 3 No salted broth or extra juices or extra milk.
- 4 No "vegetable" salt, no soda for "gas."

* A "neutral" diet is not a low-salt, or low-sodium, or acid-ash diet, but a combination of all three, and the diet reaction is, within limits, more important relatively than the total sodium or salt. Therefore each meal or feeding is balanced, and if any acid-ash item is not eaten an equivalent basic-ash item must be omitted. The diets are based on the Newburgh-MacKinnon tables.⁸

Initial Neutral Diet
Six Small Feedings, with Protein 60-70, Calories 2400

Food	Wt	Measure	Food	Wt	Measure
	gm			gm	
1 Cereal and Cream			2 Eggnog		
Cereal prepared	15	$\frac{1}{2}$ cup	One egg	—	—
or uncooked	15	1 tbsp	Milk	100	$\frac{1}{2}$ cup
or cooked	100	$\frac{1}{2}$ cup	Cream 20%	100	$\frac{1}{2}$ cup
Cream 20%	100	$\frac{1}{2}$ cup	Sugar and spice	—	—
Sugar	10	2 tbsp			
3 Fruit, Bread and Milk			4 Corn Soup		
Prunes	100	$\frac{1}{2}$ cup	Corn puree	70	$\frac{1}{2}$ cup
Bread	30	1 slice	Bread	30	1 slice
Butter	10	1 pat	Butter	10	1 pat
Milk	200	1 cup	Cream	70	$\frac{1}{2}$ cup
5 Eggs, Toast and Milk			6 Bread and Milk		
One egg	—	—	Milk	200	1 cup
Bread	30	1 slice	Cream 20%	30	1 tbsp
Butter	10	1 pat	Bread	60	2 slices
Milk	200	1 cup	Butter	15	1 tbsp
Cream	30	2 tbsp			

Notes Whole wheat bread prepared without salt, butter to be unsalted or washed
 Cereal prepared without salt, farina, cornmeal, cracked or ground whole wheat, oatmeal, puffed rice or puffed wheat only
 Any one feeding may be repeated or substituted for another, but the two eggs and the milk for the day must be taken. Extra bread, cereal and eggs may be taken if patient is not overweight
 When digestion is weakest prunes should be souffled and the corn soup feeding replaced by feeding 6
 When digestion is stronger plums and cranberries may be used in addition to prunes, and chicken, fresh fish or lamb substituted for the egg in 5
Additional Liquids Weak tea or coffee with sugar, unsalted weak chicken or beef broth. Prunes, plum and cranberry juices well diluted in water (1:1). Water flavored with fruit flavoring (Kool-Aid, etc.)
Desserts Clear jello, wine jelly, angel food or sunshine cakes, as desired

Precautions for Home Use

1. No food or drink other than above. All of each feeding must be eaten
2. No salt substitutes except the Ammonium Chloride furnished you
3. No soda or alkali medicines for "gas" or indigestion other than the Calcium Carbonate furnished you
4. Measure out three quarts of water and take by 7:00 p.m.
5. Take two to five drops of the liquid medicine furnished you in a glass of water every hour until 7:00 p.m.

FULL NEUTRAL DIET

(Low-Sodium, Acid-Ash, Calories Unrestricted)

Foods Unrestricted as to Amount (from which at least two or three servings must be taken for any one meal)

Eggs: Two equal or one serving (which can be substituted for a meat serving)

Meats: Meat, fish or chicken (one serving is about $\frac{1}{4}$ lb. a day)

Bread: Plain breads without nuts or raisins. Whole wheat bread, puffed wheat cereal food servings as indicated, at each day.

Cereal These only (one serving a day at least)—oatmeal, farina, quick-cooking cream of wheat, cracked or ground whole wheat, corn-meal mush, hominy, puffed rice or puffed wheat, "muffetts"

Cereal Foods Servings may be taken at any meal and must be taken if meat or egg is not eaten macaroni, spaghetti, rice, home-made noodles, corn

Fruit Prunes, plums and cranberries For other fruits, see below

Foods Restricted as to Amounts (from which no more than two servings should be taken for any one meal)

Vegetables Two servings a day of $\frac{1}{2}$ cup each of any vegetable except parsnips, lima beans, rhubarb, chard and spinach, which are forbidden One small potato equals a serving Use fresh or frozen vegetables or those canned without salt

Fruit One serving of $\frac{1}{2}$ cup of fruit or fruit juice daily except raisins and dates which are forbidden

Salads of fruit or vegetable may be made from the above, as desired

Raw fruit and raw vegetable should be used several times a week

Milk and Milk Products Two cups of milk daily, including that used in preparing food Cream two tbsp in coffee or tea, $\frac{1}{4}$ cup for breakfast cereal Ice Cream Without fruit or nuts, one small scoop in a day Cheese Only unsalted, cottage cheese (which may be substituted for a meat or egg serving)

Other Foods and Food Combinations

Soups May combine vegetables, as allowed above, with milk allowance or with salt-free broth to make soups Salt-free clear beef or chicken broth may be taken as desired both with and between meals

Desserts No limits as to amount Plain jello, wine jelly, plain tapioca, angel food or sunshine cake. (No cake or cookies made with salt, soda or baking powder)

Limited by milk allowance above Custard, junket, cornstarch pudding, egg-nogs, ice-cream Fruit as indicated above

Beverages One cup of tea or coffee to each meal, chocolate made with milk allowance (See Precautions for Neutral Diets)

Neutral Foods Which may be taken in any quantity desired Sugar, butter, oil, gelatin, salt-free salad dressing, plain tapioca and plain cornstarch, clear sugar candies

Sample Menu

Breakfast

$\frac{1}{2}$ cup orange juice
1 soft boiled egg
and/or cereal
 $\frac{1}{4}$ cup cream
Toast, 1-2 slices
Coffee

Lunch

Corn soup
1 poached egg
on toast or
Buttered noodles
Lettuce salad
Bread
Milk, 1 cup
 $\frac{1}{2}$ cup baked custard

Supper

Roast beef
1 small baked potato
 $\frac{1}{2}$ cup asparagus
Bread
Coffee
 $\frac{1}{2}$ cup plums

PRECAUTIONS FOR "NEUTRAL" DIETS

- 1 No salt or soda to be used in the cooking or at the table
Small amounts of ammonium chloride may be used as a salt substitute
Use no other salt substitute, such as "vegetable" salts (Eka, etc)
- 2 Obtain unsalted sweet butter or wash butter free from salt
Obtain unsalted bread from baker, or make at home
Unsalted salad dressing must be made at home
- 3 Take no salted appetizers or salted foods such as salted nuts, potato chips, sardines, olives, pickles, relishes, no cheese except unsalted cottage cheese, no smoked or salted meats or fish such as canned salmon or tuna, bacon (unless par-boiled), ham, lunch meats, sausage, salt pork
- 4 For "gas" or "indigestion"
Take no bicarbonate of soda and no alkali powders or tablets (Tums, etc, etc)
Use calcium carbonate only
Avoid cabbage family, turnips, rutabagas, peppers, radishes, onions, spices, greasy fried foods and pork

5 *For extra liquids*

Take none of the vegetable juices or fruit juices on the restricted list, or milk or salted bouillon

Use only well diluted plum, prune or cranberry juice, or water with fruit flavoring (such as Kool-Aid) or unsalted chicken or beef broth

FULL NEUTRAL REDUCTION DIET

(1,000 Calorie)

Food *	Amounts	Breakfast	Sample Menu
Fruit	See list		Orange juice
Cereal (skimmed milk)	$\frac{1}{2}$ cup		
or			
Toast	1 slice		Toast
Egg	1		Egg
Butter	$\frac{1}{2}$ teaspoon		Butter
		Lunch	
Eggs or	2		
Lean meat, fish or chicken	1 serving (2 oz)		Sliced chicken
Vegetable	See list		Tomatoes and lettuce
Bread	1 slice		Bread
Butter	$\frac{1}{2}$ teaspoon		Butter
Milk (skimmed)	$\frac{1}{2}$ glass		Milk
		Supper	
Fish, lean beef,	1 serving (3 oz)		Roast beef
chicken, lamb, veal,			
or mutton			
Vegetables	See list		Peas
Fruit	See list		Plums
Milk (skimmed)	$\frac{1}{2}$ glass		Milk
Bread	1 slice		Bread
Butter	$\frac{1}{2}$ teaspoon		Butter

* Notes on the FOOD

Fruits Prunes, plums or cranberries must be used for one of the two fruit servings
Cereal Use only oatmeal, farina, ground whole wheat, puffed rice or puffed wheat
Bread Whole wheat bread preferably (May use as substitute for one slice of bread
 $\frac{1}{2}$ cup of rice, macaroni, noodles or spaghetti)
Tea and Coffee Clear or with saccharine as desired

List of Vegetables and Fruits Only these, in the amounts shown, are permitted

One Half Cup Amounts			Other Quantities	
Endive	Lettuce	Green pepper	Cabbage family	$\frac{1}{2}$ cup
Radish	Squash	Egg plant	Tomatoes	$\frac{1}{2}$ cup
Watercress	Turnips	Mushrooms	Tomato juice	$\frac{1}{2}$ cup
Onion	Peas		Asparagus	$\frac{1}{2}$ cup
Pumpkins	String beans		Corn	$\frac{1}{2}$ cup
Lemon juice		Peach	Grape juice	$\frac{1}{2}$ cup
Grapefruit, or its juice		Grapes	Fresh prune	$\frac{1}{2}$ cup
Orange, or its juice		Apple	Melon	$\frac{1}{2}$ cup
Raspberry		Strawberries	Pineapple	$\frac{1}{2}$ lb
Pears		Apricots	Berries	$\frac{1}{2}$ lb
Blueberries				

(Fruits should be fresh or canned or cooked with water)
 (Vegetables should be fresh, frozen or canned)

Not to be used for

"Precautions for Neutral Diets" must be appended here as on the "Full Neutral Diet" above
(This "neutral" diet has been useful in cases of simple obesity which are not losing weight properly due to "water retention," i.e., sodium retention)

SAMPLE HOSPITAL ORDERS

A For massive anasarca with no great mechanical embarrassment from the edema and no great trouble in eating or drinking

- Orders
- 1 Initial neutral diet
 - 2 Intake to 4,000 c.c. daily
 - 3 Diluted HCl M 5 in a glassful of water every hour until 7 00 p.m.
 - 4 Ammonium chloride gr viiss (enteric coated) 1 tablet t.i.d.
(or 1 tablet after each of the six feedings)
 - (5) If needed to bring intake to 4,000 c.c., 500-1,000 c.c. of 5 per cent glucose in distilled water i.v.

B For massive anasarca with marked embarrassment from the edema and with inability to take significant amounts of liquids

- Orders
- 1 Water orally as tolerated with 2 drops of diluted HCl to each glass
 - 2 500 to 1,000 c.c. 5 per cent glucose in water i.v. at 7 a.m., 1 p.m., and 7 p.m.
 - 3 Mercupurin 1 c.c. i.v. second hospital day
 - (4) Begin orders under A as soon as possible

It is assumed that appropriate methods for the treatment of the primary disease and its symptoms are in force. Total intake and output are routinely recorded for 24 hour periods terminating just before breakfast, at which time the patient is weighed daily when possible.

Only when the dietitian and the nursing force are familiar with the details of the regime and the precautions to be exercised, will simple orders such as those above be sufficient to put the regime into effect.

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ORIENTATION OF TREATMENT IN THROMBO- PHLEBITIS, PHLEBOTHROMBOSIS AND PULMONARY EMBOLISM *

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THE treatment of venous thrombosis is very much a method of "dam if you do, damned if you don't" One is never quite sure which case develop a fatal pulmonary embolism Out of the welter of confusion on subject, however, are evolving certain principles which seem reasonable which may need revision in the future

In the first place, there are now four new well accepted therapeutic procedures, venous ligation and section, paralumbar sympathetic plexus block, anticoagulant therapy and sulfonamide drugs I shall attempt point out in what type of venous thrombosis each method seems most applicable

One may quote statistics pointing out that most patients with fatal pulmonary embolism die without warning and without premortem evidence of any phlebitis in the extremities where it might be detected and the physician be forewarned This is true to a degree, but I am convinced that a greater degree of consciousness of this possible eventuality would lead one to discover warning signs Again and again after a benign pulmonary embolism thrombophlebitis of a leg vein has become apparent, questioning will bring forth the reply from the patient, "Oh yes, I had a little pain in my calf yesterday but thought it was stiffness from lying in bed." Or review of temperature chart brings forth the fact that the patient had run an unexplained, low grade septic fever two to three days before the embolism occurred. Therefore all fat patients, patients with sluggish circulations, above all with histories of previous thrombophlebitis following childbirth surgery, upon whom have been performed cholecystectomies, herniotomies, hysterectomies, Mikulicz operations, colectomies, or Miles resections, should be routinely examined for a positive Homans' sign, pain in the calf, swelling of the legs, and low unexplained septic fever, especially during the critical eighth to sixteenth postoperative days

A properly conducted dawn patrol will prevent a Pearl Harbor prophylaxis is the best cure Of all measures I believe bicycle exercise faithfully supervised by the nursing staff are the most effective The past winter (and why do these epidemics of pulmonary embolism come in winter time?) there were four patients with pulmonary emboli and two with thrombophlebitis, a total of six cases, in one of our hospitals, contrasted with 14 patients with venous thrombosis with or without pulmonary emboli in another hospital, the latter hospital having by actual count a larger number

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only 10 per cent more active. In the first of these hospitals, bicycle exercises were most assiduously supervised by the nursing staff, but in four cases in which thrombophlebitic complications occurred these exercises had been deferred, because of a vulvectomy in one, and because of clamps to the bowel in the three others. We are now changing our routine to a gentle range of bicycle motion in such cases not believing the danger to clamps to be as great as that from stagnant circulation in veins. For cases suspected of developing thrombophlebitis we include in our routine ace bandages to the legs, a cradle of lamps, and avoidance of flexing the thighs on the abdomen. It is well worth while to go down the ward pulling pillows out from under the knees of patients. Reduction of weight before performing operations of choice is a very valuable procedure.

These constitute our measures to prevent sudden death by pulmonary embolism which may occur without any warning. Such emboli metastasize from pelvic veins or from leg veins at the moment of their formation before local signs have developed. One other prophylactic measure is to be mentioned—mass anticoagulant therapy of our surgical hospital population, first by heparin which is far too expensive, and second by dicoumarin, which is still experimental, and which in my hands has proved too erratic and too dangerous. In 25 cases I have had one death, one barely saved from death by repeated transfusions, and two other minor hemorrhages (hematuria and gluteal hematoma). The doses used in these patients who suffered hemorrhages were no greater and were often less than in the patients who failed to respond with prolongation of coagulation time. An intravenous salt of dicoumarin given once in 24 or 48 hours may prove more reliable by avoiding the element of variability in absorption.

We now come to the question, what shall be done for the patient who has obvious phlebothrombosis or thrombophlebitis, or the patient who has already had a warning benign pulmonary embolism of unknown source or from a pelvic venous thrombosis. Here the "damned if you do and damned if you don't" comes in.

There are five methods of treatment available, one old—heat, elevation, immobility of an involved limb and rest, three new—(1) ligation and section, (2) paralumbar sympathetic procaine block, (3) anticoagulant therapy with heparin, dicoumarin or a combination of both, and (5) sulfonamide drugs. The value of these procedures cannot be determined until mass statistics are available, and I have none. However, certain experiences stand out in my mind. I have seen a patient after two courses each of 10 days of heparinization die of pulmonary embolism one hour and 25 minutes after stopping the heparin because the femoral vein was not ligated when he had two warning benign pulmonary emboli. I have seen another die of progressive clotting in the pelvic veins extending up into the inferior vena cava after ligation of the femoral vein following a warning benign pulmonary embolism, and this progression occurred because anticoagulant therapy had not been used. I have seen a patient return with a badly swollen leg which

had not swollen in the hospital during bed rest and heparin therapy, and this swelling probably could have been prevented by paralumbar sympathetic procaine block. In this patient, belated block fortunately greatly alleviated pain and swelling, as I have sometimes seen it do even 19 months after the original thrombophlebitis.

Venous thrombosis falls into six classifications, and each type is fraught with different dangers as regards likelihood of pulmonary embolism. Here we deal with the problem of the clinician facing a recognizable, developed lesion and wondering what to do in order to prevent a pulmonary embolism from occurring or recurring as the case may be.

1 *Phlebothrombosis* (Ochsner). This type, occurring in the calf veins, often with no swelling and only slight or no fever, with soreness in the calf and pain in the upper calf on flexing the foot as in eliciting an ankle clonus (Homans' sign), often first gives evidence of its presence by pulmonary embolism. Tenderness may already be present or soon appear in the saphenous triangle. This type is common following abdominal or pelvic surgery and is dangerous as regards pulmonary embolism. If the patient is over 50 and a warning embolism has occurred, I believe this is the prime indication for ligation and section of the femoral vein. Administration of heparin should be immediately instituted after ligation and section because other veins may already be involved or become involved and emboli be cast off from them. Indeed, it is quite probable that a second embolism in such cases probably comes more often from a second focus of venous thrombosis than from the already organized clot in the recognized focus. This thought leads some to cast doubt on the necessity of ligation of the femoral vein. However, experience with a patient who had multiple pulmonary infarcts at first diagnosed as coronary occlusion and who ceased having such accidents after ligation and section of a thrombosed femoral vein, and another patient who at postmortem examination showed the only possible source of his infarct to be the original thrombus in the femoral system have confirmed to me the value of this procedure.

2 *Venous Thrombosis of the Pelvic Veins*. This location seems to me the most dangerous source of pulmonary emboli by a ratio of about 3:1 in comparison to leg veins. Here there may have been only two to three days of a warning low septic fever and then a large pulmonary infarct occurs. The best treatment is by anticoagulants. We have now successfully treated 11 of these patients by combined heparin and dicoumarin (none of the accidents quoted above occurred in this group of cases with combined therapy). The heparin is given for immediate effect, and the dicoumarin

embolism than the older recognized thrombus, and it will prevent propagation of an embolus in the pulmonary arteries

3 *Thrombophlebitis of the Femoral System* (Phlegmasia alba dolens or "milk-leg") This is an inflammatory process involving the whole sheath including the arterial sheath and perivascular network. The thrombus is tough and adherent, and emboli rarely occur except sometimes very early in the process before the leg is recognized as a "milk-leg." Hence ligation and section are not necessary in this lesion. The prime indication is paralumbar sympathetic procaine block with simultaneous anticoagulant therapy. The block is to be regarded as symptomatic treatment, abolishing reflex arterial spasm, thereby increasing arterial circulation which in turn enhances lymph circulation, reduces swelling, abolishes pain, and greatly shortens convalescence. The anticoagulant therapy prevents extension into the pelvic veins and propagation of the same process in the opposite leg.

4 *Superficial thrombophlebitis migrans* in the saphenous system in my experience never causes pulmonary embolism except by extension into the deep femoral system. Therefore, this must be watched for carefully. I have seen two such patients die from fatal pulmonary embolism. One of them occurred after tying the saphenous vein following a warning benign embolism, when the femoral should have been ligated and sectioned. In the other, postmortem examination showed extension into the deep femoral system. If the phlebitis remains superficial, as it usually does, an ace bandage, rest off the feet but not bed rest, and sulfathiazole are the treatment of choice. If the phlebitis remains for a long time in one vein, one is justified in ligating this superficial vein well above the inflammatory process simply in order to isolate the lesion. Anticoagulant treatment may be used in especially stubborn cases as these cases may recur in migratory forms over months.

5 *Thrombophlebitis in varicose veins* rarely requires more than local heat, rest and compression bandages if not too painful. Pulmonary emboli do not occur from varicosities, and but rarely is there progression into the deep system.

6 *Thrombophlebitis of the upper extremities* is comparatively rare. I have seen only three cases. In one of these, multiple pulmonary emboli did occur. This case occurred in the days before heparin. The patient also had thrombophlebitis in the legs, and the source of the emboli may have been the leg or the pelvic veins. Some authorities declare this is a dangerous source of pulmonary embolism in the cardiac patient. However, I doubt if it is in younger people who have acquired the lesion from traumatic causes. The greatest danger is extension into the jugular vein or superior vena cava. Anticoagulant therapy and sulfathiazole are the treatment of choice. I see no reason why cervical sympathetic procaine block might not be used to reduce swelling. I do not believe that subclavian ligature is indicated except perhaps in the cardiac over fifty who has had a warning pulmonary embolism.

I have made no mention of leeches with which I have had no experience.

CONCLUSIONS

1. Deep phlebothrombosis of the femoral or calf venous plexi is a dangerous source of pulmonary embolism. If the patient is more than fifty, ligation and section of the femoral vein should be seriously considered. It cannot be emphasized too strongly in cases of this type that if there has already been a warning embolism, ligation and section of the femoral vein, or if need be, the external iliac vein, is indicated.

2. Phlebothrombosis in the pelvic veins is a dangerous source of pulmonary embolism. Prolongation of the clotting time by heparin or dicoumarin or both prevents propagation of a clot in the pulmonary artery should embolism occur.

3. In phlegmasia alba dolens, lumbar sympathetic procaine block is the treatment of choice. The earlier this procedure is performed the better, although the results obtained in chronic cases may be surprising. There is relatively little danger of pulmonary embolism in typical "milk-leg."

4. Thrombophlebitis migrans, thrombophlebitis of the upper extremities, and the thrombophlebitis of Buerger's disease rarely cause pulmonary embolism. However, propagation of the clot into the deep veins of the leg must be carefully watched for in phlebitis migrans. Isolation of an involved segment of vein by ligation may be necessary. Compression bandages, rest, and sulfathiazole are of value. Heparin or dicoumarin may be needed to stay progression of the clot in cases of thrombophlebitis in the upper extremities.

INTRACUTANEOUS INOCULATION OF POLIO-MYELITIS VIRUS IN MONKEYS AND ITS DETECTION IN THEIR STOOLS *

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IN order to learn if the virus of poliomyelitis can be detected in monkeys' stools after it has been inoculated intracutaneously the experiment presented in table 1 was performed. It may be described as follows.

On April 2, 1941, stools were collected from 10 monkeys representing four (or five) different species and one chimpanzee. The animals were then inoculated intracutaneously with the SK strain of virus (generation XIV) from monkey No 17-66, a green African monkey. Injections were made in 10 piqures in the left flank with 2 c c of a 10 per cent suspension of glycerolated cord. The inoculated animals were placed in six separate cages according to species, and observed for the signs of experimental poliomyelitis. Daily rectal temperatures were recorded except for the chimpanzee which was exercised but not handled and which was kept in a separate building where there were no other infected animals. Thus the chances of unexpected contamination of stools were reduced with the chimpanzee. Stools were collected daily from each cage, refrigerated at 6° C until a week's store was on hand, which was then pooled for storage according to species, and kept in an insulated box with dry ice. Green African monkeys¹ were used principally to test the stools for virus. For these tests 2 c c of 10 per cent stool suspensions were instilled intranasally on three successive days and at first 5 c c of etherized centrifuged suspension were also injected intraabdominally. With the first batch of seven stool tests there was an accidental loss of four green monkeys, and so in subsequent tests the intranasal inoculations alone were used as indicated in the legend of table 1. For controls a pool of all the premoculation stools collected before the intracutaneous injections was tested in one monkey, and tests on premoculation stools of three individual species (green and mona monkeys, and the chimpanzee) were also done. These controls appear in the first and second columns of table 1. In addition to tests with postinoculation stool suspensions, five tests of rectal swabbings (from monkeys 16-71, 18-13, 18-14, 17-98, and 17-99) by direct individual intranasal inoculations into three cynomolgus and in two green monkeys were made. These tests were negative and they appear in the column for the third week in table 1.

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† Deceased.

TABLE I

Intracutaneous Inoculation of Poliomyelitis Virus into Monkeys and Its Occasional Detection in Their Stools

Preinoculation Period Tests for Virus in Stools		Poliomyelitis Virus Inoculated Intracutaneously						Postinoculation Period Tests for Virus in Stools			
		Apr 2, 2 c.c. 10% SK Strain			Experimental Poliomyelitis			Weeks After Inoculation			
General Pool	Individual Species	Species	Monkey No	Cage	Paralysis	Remarks	Path CNS	1	2	3	4
(-)*		<i>M. irus</i> (<i>Cynomolgus</i>)	16-70 16-71	1	++ -	Died April 9 Tuberculosis	++ -	(-)*	-	-	
			18-31 18-32	2	- -	Tuberculosis Tuberculosis	- -	(-)	(-)		
		<i>M. mulatta</i>									
		<i>M. irus</i> (<i>M. mordax</i>)	18-34 18-33	3	++ +	Dying, killed April 18	++ +	(-)	(-)		
	(-)		18-13 18-14	4	+ +		§ +		(-)	-	
		<i>C. mona mona</i>									
	(-)	<i>C. ethiops</i> <i>sabaeus</i>	17-98 17-99	5	+ +		+ 0	(+)*	(-)	-	
	-*	<i>Par. satyrus</i>	18-58	6		Agitation and tremor 2nd week	§	+*	+		-*

() Pool of stools of 2 or more monkeys

§ Immune to reinoculation November 6, 1941

0 Not examined.

* Intranasal and intra-abdominal inoculation.

The criteria for a positive stool test consisted in (a) the production of the usual signs of experimental poliomyelitis with flaccid paralysis of one or more extremities, and (b) the demonstration of classical histological lesions with vascular cuffing in upper and lower levels of the spinal cord. In the positive test with the first week's stools from the green monkeys, passage was also secured, and the virus used for this purpose was not infective for mice and guinea pigs on intracerebral inoculation.

The results shown in table I reveal that 14 of the 15 inoculation tests were negative and that three were positive. The virus was detected in the pooled stools of green monkeys 17-98 and 17-99, collected in the first post-inoculation week and in the chimpanzee's stools collected in the first and

in other experiments ^{8, 4} Green monkeys 17-98 and 17-99 had typical mild paralytic poliomyelitis, and virus was found in their stools in the first week. The monas and one mordax had mild poliomyelitis and no virus was found in their stools. The mildest infection appeared in the chimpanzee, although her stool tests were positive twice. She had transitory agitation and tremor during the second week. She was able to walk normally and no paralysis could be made out on inspection, although at present she may have some atrophy of her hind legs. She has not been sacrificed. She was reinoculated seven months after her first inoculation and appeared immune, but the nature of this apparent immunity is not entirely clear. The test was as follows: she and a "normal" mate received the SK strain intracutaneously November 6, 1941 and developed no symptoms, although two normal cynomolgus and one normal mona contracted fatal poliomyelitis while the convalescent mona (18-13 of table 1) remained unaffected.

Returning to the experiment of April 2, the three tuberculous monkeys developed no signs of poliomyelitis, and we have noted before that tuberculous monkeys have been partially resistant to experimental poliomyelitis. It is therefore unfortunate for the sake of the comparative study that both the *M. mulatta* were tuberculous. Previously *M. mulatta* has proved less susceptible to cutaneous infection than the green monkey ¹

COMMENT

When monkeys and chimpanzees have been fed poliomyelitis virus, it has been recovered from their stools or intestinal contents by Levaditi, Kling and Lépine ⁵, Clark, Schindler and Roberts ⁶, Clark, Roberts and Preston ⁷, Flexner ⁸, Howe and Bodian ⁹, and Sabin and Ward ¹⁰. After intracerebral inoculation, demonstration of the virus in stools of *M. mulatta* has failed according to Clark, Roberts and Preston ⁷, and according to Howe and Bodian ⁹. Virus was detected in upper intestinal contents of *M. mulatta* once, by Kramer, Hoskwith and Grossman, ¹¹ but it is difficult to know whether this was after intranasal or intracerebral inoculation.

The present report is the first known to us of the detection of the virus in feces during the experimental disease apparently induced by intracutaneous inoculation. Possibly this indicates that the hands and thereby the mouths of the animals may have become contaminated. We do not hold this view, but even if it were true, the fact that virus may be applied to the skin and later detected in stools would still be important. However, it is unnecessary to postulate external contamination, because in another series of experiments (but not in this series) well marked lesions were found in the olfactory bulbs in one cynomolgus and one green monkey inoculated intracerebrally and intraabdominally but not intranasally with the SK strain. Moreover, Sabin and Ward ¹² have detected the virus of poliomyelitis in the blood of cynomolgus monkeys paralyzed after oral infection with a strain

of recent human origin. Therefore, it appears that virus may spread in these species by paths as yet ill defined.

We believe that the positive results described in this report are dependent upon the particular strain of poliomyelitis virus used and the particular species of monkey tested. The results also suggest that the intracutaneous inoculation of virus may be a useful method for the comparative study of experimental poliomyelitis in different species.

CONCLUSION

1. Following the intracutaneous inoculation of the virus of poliomyelitis into monkeys it may be detected occasionally in their stools.

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THE ARMY'S NEW FRONTIERS IN TROPICAL MEDICINE *

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INTRODUCTION

THE United States Army is now engaged in an "all-out" war in the tropics. Since December 1941, American soldiers have been sent to new frontiers scattered throughout the tropical regions of the world. On these frontiers, they face powerful enemy forces and an alarming array of tropical diseases. Certain of these diseases are potentially so disabling that unless controlled they will interfere with military efficiency, in fact it is conceivable that they might play a significant rôle in determining the final outcome of the war. The protection of our troops against such diseases is, therefore, of vital importance, and the maintenance of an effective program for their control is a responsibility not only of the medical personnel of the armed forces but of the entire medical profession. With this common obligation in mind, it is proposed (1) to define the term "tropical diseases", (2) to indicate briefly the extent of the Army's past experience with such diseases, (3) to discuss the development of the present program for their control, (4) to estimate the effectiveness of this control program, and (5) to suggest certain ways in which it can be improved.

Definition of Tropical Diseases ' According to Sawyer, "a tropical disease is any disease as it behaves in a tropical environment." His statement was modified as follows. "The natural tropical environment is not definable in terms of heat and humidity. It is really a thousand different and complex environments, occurring, to be sure, in the warmer parts of the earth, but compounded of special local conditions of climate, social make-up of the people, social and economic conditions, food materials and especially the arthropod vectors of disease and animal hosts."

This broad concept is excellent, but for our purposes it seems preferable to limit tropical diseases to the following categories: (1) diseases such as malaria, which may be endemic in either tropical or temperate climates, but are more prevalent in the tropics, (2) filth diseases such as the dysenteries and cholera, which are more common in tropical countries because of the poor sanitary, hygienic and climatic conditions which prevail in many such regions, but which may cause epidemics when introduced into temperate climates; (3) diseases which are normally limited to endemic centers in certain tropical regions, but may spread to and cause epidemics in temperate countries, as for

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example, yellow fever; and (4) diseases which originate in and are limited to tropical regions, as for example, African sleeping sickness

The Army's Past Experience with Tropical Diseases During the century and a half of our national existence, the Army has had a rich experience with tropical diseases both at home and abroad

In the United States In the Continental United States troops have always been exposed to such endemic diseases as the dysenteries, other enteric infections, and malaria Before the present century, they were frequently attacked by epidemics of yellow fever, cholera, and other exotic diseases, introduced from abroad Such infections have been most prevalent in the southern states, but at times they have occurred in the north As is usual, they caused more damage during periods of war than in times of peace

In Foreign Countries Our soldiers have also been exposed to tropical diseases while on duty outside the United States During the nineteenth century, such diseases were important causes of sickness and death among the American forces engaged in the Mexican and Spanish-American Wars In the Mexican War, disease caused seven times as many deaths as did battle injuries During General Scott's campaign in Mexico, the losses from disease alone exceeded 33 per cent of the effectual strength of his forces. The prevalent infections were dysentery, typhoid and malaria, but yellow fever and cholera were also present During the war with Spain, we also lost seven men from disease to every one killed in battle One-fifth of the troops developed typhoid fever, and this disease caused 80 per cent of the total deaths Malaria produced a death rate of 2.7 per 1000 and after the capture of Santiago in 1898, it incapacitated half of our forces in Cuba There were about 1500 cases of yellow fever with 200 deaths

By the end of the nineteenth century a number of the causative agents of disease had been identified Manson (1878) had discovered the mosquito transmission of filariasis; Theobald Smith and his associates (1892) had incriminated ticks as the vectors of Texas cattle fever; Bruce (1895) had identified the trypanosome of "nagana" in African horses and cattle; and Manson, Ross, Grassi and others had proved that human malaria is transmitted by Anopheline mosquitoes However, the epidemiology of many infections was still unknown or imperfectly understood and military hygiene and sanitation were neither well-developed nor generally appreciated The lack of basic medical knowledge was clearly reflected in the high infection and death rates.

During the 43 years which have elapsed since the Spanish-American War, great progress has been made in military tropical medicine. Immediately after the war, the United States acquired its first tropical possessions, and the Army established permanent garrisons in the Philippine Islands, Guam, Hawaii, Puerto Rico, and later in the Panama Canal Zone In pre-occupied with the health hazards to be encountered, George M. Sternberg, the Surgeon General, organized special boards of officers to study the diseases of tropical and these newly acquired possessions.

The Board, formed by Walter Reed in Cuba, soon confirmed Carlos Findlay's experiments dealing with the mosquito transmission of yellow fever, thus indicating effective methods for the control of this disease. Richard P. Strong and the medical officers who succeeded him on the Board in the Philippines, including Craig, Vedder, Siler and others, made valuable contributions to our knowledge of cholera, the dysenteries, beriberi, plague, malaria, filariasis, dengue fever, and other diseases. Bailey K. Ashford in Puerto Rico showed that the local disease known as "Malignant Puerto Rican Anemia" was caused by massive hookworm infestation and started a control program which was a forerunner of the world-wide hookworm campaign conducted by the Rockefeller Foundation. Gorgas and his associates, armed with newly acquired knowledge about the mosquito vectors of yellow fever and malaria, were able to sanitize Havana and later the Canal Zone against these diseases, Russell at the Army Medical School produced an effective vaccine for typhoid fever, and Darnall developed a method for the chlorination of water supplies, which is now used in most of the large cities of the world.

These and other Army contributions and the innumerable researches carried on by other scientists all over the world afforded a valuable fund of basic information concerning the etiology, treatment and prevention of tropical diseases. With this information, it has been possible to develop methods for the protection of troops against infections both at home and abroad. Naturally these control methods were more effective under peace-time conditions in permanent garrisons than in the field during maneuvers or campaigns.

Since 1900 the Army has been increasingly successful in the control of all diseases including those of the tropics. During World War I, there was a temporary increase in the total disease rates due mainly to the influenza epidemic, but as our forces operated mainly in temperate regions, the only tropical disease of importance was malaria and this infection was well-controlled. However, as is shown in the following charts, there has been a spectacular decrease in the Army's peace-time admission and death rates for all diseases, and in 1939, these rates reached the lowest points ever experienced by the United States Army.

Development of the Present Program for the Control of Tropical Diseases As the United States passed through the recent period of rapid mobilization into the present state of war, the Army acquired many new tropical frontiers. In 1940, when the Caribbean bases were obtained from Great Britain, our frontiers were extended to Bermuda, Jamaica, Antigua, St. Lucia, St. Kitts, Trinidad, and British Guiana. Since our declaration of war, they have been extended further by the transfer of military forces to other tropical countries in the Western Hemisphere and in Africa, Asia, Australia, the East Indies and elsewhere. Throughout this period the Medical Department has been actively engaged in the perfection of plans for performing all of its functions efficiently under such conditions as might

arise Naturally, preventive medicine has had an important place in these plans Arrangements have been made to strengthen all our existing health facilities by expansion, modification, or when indicated, by the adoption of

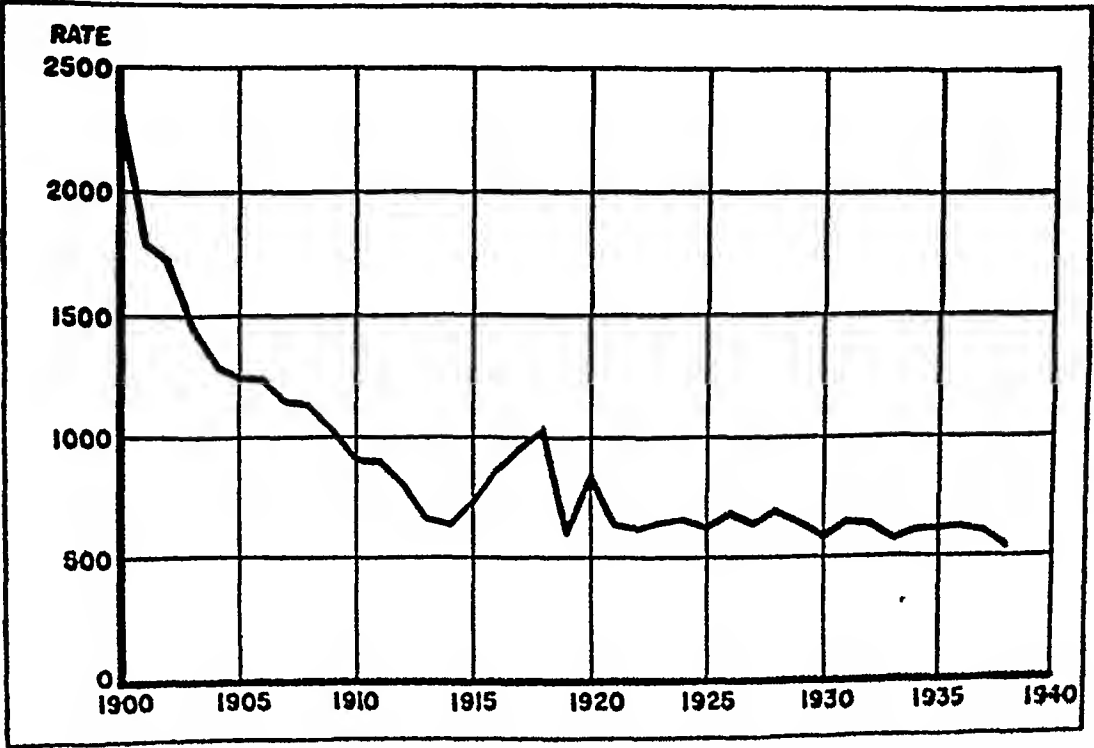


FIG 1 Admissions, U S Army, 1900-1939 Admissions to sick report, officers and enlisted men, all causes excluding battle injuries, annual rates per 1,000 strength, since 1900

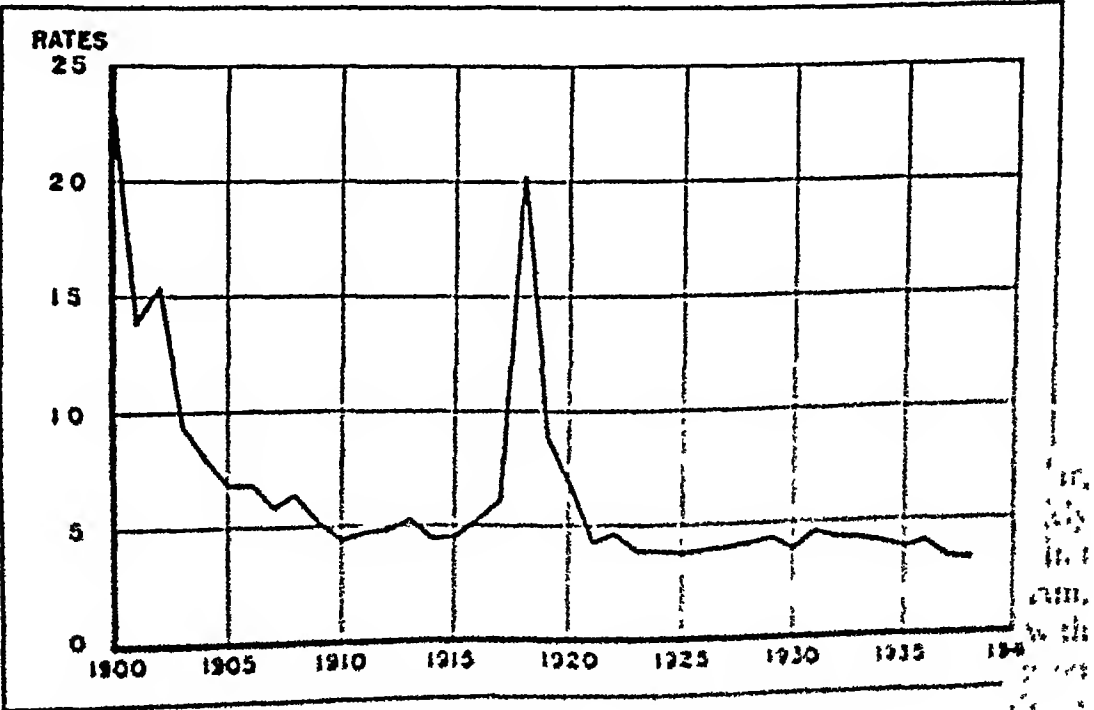


FIG 2 Deaths, U S Army, 1900-1939 Deaths from all causes excluding battle injuries, annual rates per 1,000 strength, since 1900

new procedures As our military interests spread to these new regions, greater special emphasis was placed on the control of tropical diseases

Certain special features of the control program which has been adopted by the Surgeon General are indicated below

(1) Since the early part of 1940, there has been developed in the surgeon General's Office, a special Preventive Medicine Service which now includes Divisions of Sanitation, Laboratories, Sanitary Engineering, Occupational Military Hygiene, Venereal Disease Control, Medical Intelligence, and Epidemiology In the latter Division there is a subdivision devoted entirely to the control of malaria and other tropical diseases

(2) The Division of Medical Intelligence was formed for the purpose of collecting and analyzing current information regarding medical and health conditions in foreign countries Such information is obtained from every available source including the Pan-American Sanitary Bureau, the Rockefeller Foundation, other international and foreign health organizations and scientific publications When possible, it has been supplemented by personal interviews with informed individuals and by the reports of sanitary investigations made by medical officers sent abroad for that purpose The files of this Division now contain carefully prepared surveys on practically every country in the world This information has been used by the Medical Department as a basis for specific sanitary precautions recommended for the protection of every military force which has left our shores Such recommendations are naturally modified to meet the peculiar disease conditions of the regions to which troops are sent, for example, forces bound for certain parts of Africa would be warned against trypanosomiasis, whereas troops sent to Trinidad would require protection against the vampire bats of that region, of which about 4 per cent are vectors of rabies

(3) A civilian advisory committee on tropical diseases was organized in May 1940, by the Division of Medical Sciences of the National Research Council The members of the committee have rendered valuable advice on matters of policy and have assisted in the preparation of circular letters on tropical medicine for the guidance of medical officers throughout the service They have also helped in planning our training program and in the initiation of various research projects dealing with tropical diseases

(4) The Army's peace-time immunization program has been expanded to include vaccinations against certain diseases of the tropics At present all military personnel receive the following prophylactic injections (a) small-pox vaccine, (b) triple-typhoid vaccine, (c) tetanus toxoid, and (d) yellow fever vaccine Personnel ordered to continents where they may encounter epidemic, or louse-borne typhus are given typhus vaccine, those going to regions in which cholera exists are given cholera vaccine, and in regions in which human epidemics of plague occur, plague vaccine will be used Unfortunately, we do not know the degree of protection afforded by the typhus,

cholera and plague vaccines and, therefore, it is necessary to supplement the use of these agents by the strict enforcement of all other control measures

(5) The expansion of the Army's laboratory services now includes special epidemiological and sanitary laboratory facilities in the tropics. An attempt has been made to staff these laboratories with individuals familiar with tropical problems, but unfortunately, such qualified personnel has not always been available

(6) The health program has also been strengthened by the formation of the "Board for the Control of Influenza and other Epidemic Diseases in the Army". This Board is now composed of more than 100 civilian physicians. It is divided into nine Commissions, each dealing with a different problem. The Commission on Tropical Diseases is available at all times for the investigation of tropical infections

(7) In 1940, a group of sanitary experts was organized to safeguard the health of civilians engaged in the construction of our Caribbean bases. A difficult medical problem was presented by the employment of the thousands of civilian workers required to build the air fields and other facilities needed to advance our frontiers over the Atlantic. The effectiveness of this program is shown by the fact that the construction has not been delayed by disease and there have been no epidemics among troops sent to these bases

(8) A large number of research projects dealing with the prevention or treatment of important tropical infections have been initiated or sponsored by the Medical Department of the Army

(9) An important part of the program has been the establishment of short "refresher" courses in tropical medicine at the Army Medical School and elsewhere

In Estimate of the Effectiveness of the Present Control Program. When one considers the many regions to be occupied by American troops during this war, it seems probable that sooner or later our forces will be exposed to every known tropical disease. It would be foolhardy to attempt to predict the results of these exposures. However, one should be able to make a reasonable estimate of the situation from a brief review of the measures now available for the control of the more important diseases.

seas forces Human nature being what it is, we may expect an increase in the incidence of venereal disease among our troops wherever there is laxness in the administration of the control program

The *food and water-borne diseases* occur in all parts of the world and, being diseases of filth, they are most prevalent in countries in which sanitary precautions are disregarded and soil and water pollution are common Prior to the twentieth century these diseases constituted one of the most important causes of epidemics among military personnel, but thanks to the subsequent development of improved control measures they caused relatively little trouble during World War I *Typhoid and the paratyphoid fevers* will be encountered everywhere, but all our troops are again protected by an effective triple-typhoid vaccine similar to the one used so successfully in the last war The *dysenteries*, bacillary and amebic, are equally as widely distributed Unfortunately, we have no specific measures for their control, but the methods of water purification as practiced in the field minimize the dangers of these diseases, and recent reports of the therapeutic usefulness of sulfonamides in bacillary dysentery are encouraging It is hoped that more complete protection against bacillary dysentery can be afforded our troops as the result of investigations now in progress to develop an effective, non-toxic vaccine

Cholera is now confined largely to its ancient endemic centers in Asia, where it continues to claim thousands of victims each year However, on several occasions during the last century this dreaded disease spread over the world in great pandemic waves These reached America and produced epidemics during the periods 1826 to 1837, 1853 to 1857, 1865 to 1868, and 1870 to 1873 As late as 1911, the disease reached the Port of New York, and during World War I it occurred in Russia, Austria, Hungary, Germany and Italy Cholera is a real menace which cannot be disregarded The Medical Department has provided a cholera vaccine which is being administered to all troops sent to areas in which the disease now exists The degree of protection afforded by vaccination is not definitely known, and therefore the procedure must be supplemented by every available sanitary precaution

Sanitation is paramount, and the Army has developed highly effective facilities for insuring safe water and food to the troops, even under field conditions Therefore, these "filth" diseases should not occur in epidemic proportions among well-trained troops commanded by efficient officers, except under the most unusual circumstances

The *insect-borne diseases* constitute a large group which includes some of the most dangerous infections to be encountered in the tropics Potentially the most serious of these are plague, typhus, yellow fever and malaria

Plague has ravaged mankind since antiquity There were more than 100 epidemics or pandemics before the fifteenth century, and about 45 be-

tween the sixteenth and eighteenth centuries. During the Middle Ages, the "black death" killed one-fourth of the population of Europe, and 69,000 Londoners died of this disease in 1665. An epidemic began in Canton, China in 1895, and spread to Formosa, Japan, and India, where it continued until 1925, leaving twelve million dead in its wake. Between 1923 and 1924, 25,000 cases of plague were reported from epidemic areas throughout Africa, Greece, Asia, and several South American countries. The disease now smolders in great rodent reservoirs located in the western United States and elsewhere. From any of these places it may again attack man with epidemic fury. The measures adopted for the prevention of plague in the Army are based on the protection of troops against infected rodents and fleas, supplemented by the use of plague vaccine when required in regions in which the disease is epidemic in man. Information concerning the effectiveness of vaccination is inadequate, but intensive research on this subject is under way and it is hoped that agents of known prophylactic and therapeutic value will be developed.

Typhus fever is another ancient military scourge which has always been notorious for its production of destructive epidemics among troops. This highly fatal louse-borne disease occurs most commonly in temperate or cold climates but it also exists in the tropics. Moreover, it has been suggested that the milder, endemic or murine typhus of the warm climates might become epidemic by rapid passage through lice to man. This disease has been an important factor in almost every great war in Europe and recent reports indicate that it has again become active on many fronts.

The methods now available for the prevention of typhus are based on various sanitary and hygienic measures to prevent lousiness in troops, and the use of a typhus vaccine for forces going to certain regions in which the disease may be encountered in epidemic form.

Yellow fever also has an evil military record, especially in the Western Hemisphere, and prior to 1905 it frequently invaded the United States, producing highly fatal epidemics as far north as Philadelphia, New York and Boston. The disease is still endemic in vast jungle regions in tropical South America and Africa, and from these foci, the infection may at any time be carried by air or water to new areas where *Aedes aegypti* exist and produce epidemics in this country or elsewhere. Such outbreaks have occurred within recent years in Brazil and in the Anglo-Egyptian Sudan.

The Army's control program is based on (1) the enforcement of special precautions taken to prevent the introduction of the disease into our borders by military airplanes or otherwise, (2) the protection of troops against the bites of infected mosquitoes, and (3) the active immunization of all military personnel with yellow fever vaccine. This vaccine is prepared and supplied by the Rockefeller Foundation and the U. S. Public Health Service. Tests made subsequent to vaccination indicate that it produces a satisfactory immunity, and therefore it may be assumed that our troops will not suffer from yellow fever.

Malaria is the most widespread and the most dangerous disease to which our troops will be exposed. It is present throughout the tropics and subtropics of the entire world, and each year it causes more disability and deaths than any other infection. The Army has established an enviable record in its peace-time control of malaria among troops living in permanent stations even in our tropical possessions. During the recent mobilization, it has been possible to maintain this good record in the United States by the execution of an extensive mosquito control campaign, which in 1941 alone cost a million and a half dollars. We cannot hope for similar results among troops living in the field, even in this country, and must be prepared to meet the infinitely more dangerous problem of controlling malaria on our many new frontiers. Unfortunately we have no vaccine with which to immunize troops against malaria. Quinine or atabrin is provided for prophylactic use under certain conditions in the field. However, neither of these drugs is a real prophylactic, as they do not prevent infection but simply delay the appearance of clinical symptoms during their use. Therefore, the field control of malaria must be based primarily on the sanitary precautions required to protect men against infected mosquitoes. This is a difficult task but one which must be carried out thoroughly and unremittingly if the health of the command is to be maintained. One of the greatest medical contributions that could be made to this country at present is the discovery of a really effective agent for the prevention of malaria in the field.

Other insect-borne tropical diseases which may assume importance in various regions during this war include relapsing fever, filariasis, dengue and dengue-like fevers, Japanese river fever and other typhus-like diseases, Oroya fever, trypanosomiasis, leishmaniasis and other infections.

Theoretically, it should be possible to prevent all these insect-borne diseases by eliminating their vectors, but practically, this task is usually too enormous to be undertaken during the stress of war and under field conditions. Therefore, as only a few specific prophylactic agents are available, our chief reliance must be placed on the protection of individuals against insects.

CONCLUSION

From this general estimate of the situation, it is obvious that American troops will be exposed to an infinite variety of unusual and dangerous tropical infections during this war. It is also apparent that the degree of protection afforded our soldiers will depend on the ability of their medical officers to recognize the diseases clinically, treat them intelligently, and provide the sanitary and hygienic measures required for their control under trying field conditions. Such ability must be based on a sound fundamental knowledge of tropical medicine, including the epidemiology of tropical diseases. Since the beginning of the present emergency, the Surgeon General has been concerned with the fact that the majority of our new medical officers have not received adequate training in this subject prior to their en-

trance into the service. This lack of undergraduate training is being partially met by such emergency measures as the establishment of short, refresher courses in tropical medicine at the Army Medical School and in other Army establishments. But even this type of training is not available for all who require it, and the Army has neither the facilities nor the time to remedy so great an educational deficiency.

The solution to this problem is for the civilian medical schools to provide the required training for future medical officers. Short intensive courses in tropical medicine should be organized at once for the students of all medical classes which will graduate this summer and for the internes now in teaching hospitals. Action should also be taken to develop comprehensive courses in tropical medicine as a permanent part of the required undergraduate training in all of our medical schools.

Thus the medical educators of the United States have a unique opportunity to assist in the Army's program for the control of tropical diseases. If immediate steps are taken to provide satisfactory basic training in tropical medicine for all future medical graduates, this will not only raise the general level of medical education in this country, but will contribute materially to the safety of American troops on our new tropical frontiers.

A CONSIDERATION OF THE FACTOR OF CHANGE IN THE ANIMAL ORGANISM *

By WM DEB MACNIDER, F A C P, *Chapel Hill, North Carolina*

FIXITY of any order, even fixity of purpose, tends to bind and render inelastic the structure or the individual in which such a property develops. It is a quality which is inimicable to adaptation, and tissues or organisms without this quality of elasticity, of variability, have difficulty in meeting the exigencies of life which is made up of periods of adequate adaptation, never perfect, and periods of inadequate adaptation which may be of such a specialized nature as to produce the symptoms and later show the signs of disease.

Since 1907 the investigations in this laboratory have not been so much concerned with abnormal states as entities of disease as they have been interested in studying the changes associated with tissue degeneration and repair in a broad and, therefore, more helpful biological fashion. Certainly some of these changes may be looked upon as processes leading to adaptation, adaptation to advancing age and to maladjustments so marked that the departures from the normal have to be designated disease.

In thinking of the adjusted normal animal organism and the changes it can withstand one must conclude with a certain degree of assurance that the life span of such an individual was intended to be much longer than we now make it. I have said that "we now make it" for a purpose, for excluding physical accidents and accidents of an infectious order, the maintenance of life, its duration as well as its usefulness, are matters which we can in a large measure influence and in part determine. There are "factors of safety" within us with which we were endowed at birth that have been emphasized by Meltzer in his Harvey Society Lecture¹ for 1906. In this lecture Meltzer discusses our superabundance of tissues, far in excess of any normal demand, which through their cellular nature are endowed with the power either to increase in size upon demand or to increase numerically and further to impart to the individual great structural reserve power. This element of excess structure is furthermore shown in the dual character of certain organs and in the great power which organs, paired or unpaired, possess to take over function in the face of disease and carry on in an uninterrupted fashion the life of the individual as a whole. Such natural factors of safety have not been appreciated by us as reserves. Through excesses we have foolishly drawn upon them in their abundance for our normal way of life and depleted these factors of safety. Over-exercise, over-eating, over-worrying, more rarely over-drinking diminish these factors of endowed and natural safety, this abundant reserve tissue, and prepare us for

* Convocation Address, The American College of Physicians, St. Paul, Minnesota, April 22, 1942

the advent of tissues so different from the reserve that we designate them pathological. However, even tissues of this order may safeguard us against ourselves by furnishing us an excess of tissue which, although altered, not only functions and in part adjusts us, but at the same time endows us with a factor of resistance against further injury. The human animal organism, even with the benefit of a physician as a biological guide, romps lavishly through these normal and abnormal tissue factors for safety. This is not the case with the lower animals. They run the race for food and for sport, experience the sensation of fatigue, and permit this sensation to exercise its function in a demand for rest. The factors of safety in our abundance of tissues are severely drawn upon in order to adjust and adapt us to an artificial and exorbitant type of life which we regard as normal. The most difficult life, the most unusual and pathological one, is a "normal" one.

In addition to the factors of safety found in the superabundance of our tissues as a whole and in specialized organ structure, the animal organism, by attempting to cope with adverse conditions, has acquired certain ways of life of a functional order, automatic, and in a sense reflex in nature, which afford further protection and persist in attempting to adjust us both within and without. Cannon² designates these forces "The Wisdom of the Body." This order of bodily, automatic thoughtfulness is not concerned with changes of a structural nature, but is concerned with maintaining the varied functions of the body in a balanced and in an effective state through an interrelationship of tissue activities. These functions have to be so related to one another within the living organism that a balanced and adapted existence can be maintained by the individual in that external environment in which he has to live. Many of these changes from within which lead to at least transitory periods of adaptation to external conditions in the course of life are effected through the intervention of that part of our nervous organization, the autonomic or vegetative nervous system, over which we fortunately have no control. The balance of electrolytes in the body fluids, the maintenance of a state of chemical neutrality during life, the fixity of a constant body temperature, the assurance of an adequate oxygen supply for tissue usage, all constitute adjustments resulting from change which favor a balanced existence. These and many other balanced functional states, favorable for life and capable of withstanding strain, are maintained in spite of our willfulness to the contrary. With the factors for safety of a structural order with which the animal organism is endowed, and over and above this the capacity of the body automatically to balance and adapt us to our environment, it would appear difficult for changes of such an order to take place as to injure us permanently by the development within us of gross chemical and structural alterations. Even in those states of tissue change which are designated disease there is evidence that we may become readjusted to them at certain modified levels of physiological effectiveness. There is an inherent urge on the part of cells, not for death, but for life. The changes of degeneration which many such units can withstand and their capacity for

recuperation and repair, if given an opportunity, constitute as a composite one of the major manifestations of life

Some years ago, spurred on perhaps by the then actually non-existing state of prohibition, a period in which alcohol and aberrant alcohol beverages were consumed in large amounts, and at the insistence of certain life insurance companies, studies^{3, 4} were undertaken in our laboratory to ascertain the effect of ethyl alcohol on the liver and to observe the changes during recuperation and repair if such developed in this tissue. Ethyl alcohol in 40 per cent strength was given once a day to dogs in a sufficient amount to induce a moderate degree of alcoholic intoxication. Such a procedure was continued for from six weeks to as many months. At periods during these intoxications tissue was obtained from the liver for histological study. Observation of the liver at such periods revealed large, pale organs from the abraded surface of which a blood-tinged serous fluid readily escaped. The microscopic studies of such tissues showed the presence of liver epithelial cells in an advanced state of edema, the fluid in such cells being held in lacuna-like spaces separated by strands of cell cytoplasm. Fatty changes in such cells existed but were not marked. The dominant cell change was of such a physicochemical order that the ability of the cell cytoplasm to bind water was greatly increased, the cytoplasm increased in volume, and thereby augmented the volume of the liver as a whole. From these observations it was difficult to believe that such an organ, by changes of cell recuperation or cell regeneration, could return to a normal organ structure, and yet the only factor necessary to lead to such a normal readjustment consisted in stopping the use of the chemical, in this instance alcohol, which had made the cellular structure of this organ undergo such a departure from its established normal. Here is an instance of a chemical substance modifying cell life in terms of its form in a very extensive and abnormal fashion, and yet this tissue is still able to return to a normal state of form and function. Such a recuperative change back to a normal type of cell is not associated with the development on the part of such cells of an acquired resistance to a subsequent injury by alcohol. The factor of safety which cells possess to repair themselves by processes of recuperation must be enormous and, furthermore, such changes must be constantly going on as tissues respond to injurious agents, recuperate and readjust themselves for normal function and thus for maintaining the life of the individual as a whole. Life necessitates cellular injury, and furthermore its successful continuance depends upon the ability of such injured units to recuperate rapidly by chemical change. This capacity for change is the main factor which determines longevity and which regulates tissue accidents that may express themselves in faulty organ adaptation. Chemical injury of a given order may be the stimulus for chemical action responsible for a continuation of cell life.

In addition to these experiments which have been presented, observations of a somewhat similar order have been made when the liver was injured by agents other than alcohol^{5, 6, 7}. In these experiments the processes of repair

may be of such a nature that not only is a survival of liver tissue effected, but the liver tissue after repair may be shown to have acquired a fixed cell resistance associated with the changes in cell form that develop during the repair process. The change in cell form is not the essential element in this type of tissue resistance. The essential factor in it must be a modification of the chemical structure of the cell which is responsible for the permanent or transitory state of cell resistance.

Many years ago Whipple and Sperry⁸ made the observation that if dogs were starved for 24 hours and then given chloroform by inhalation for one hour and a half, the livers of such animals invariably developed a severe injury in the form of a fairly complete necrosis of the central one-third to two-thirds of the liver lobules. Such a standardized reaction may be easily reproduced in experimental animals. There is another liver poison, uranium nitrate, which when given in an appropriate amount to animals of a susceptible age period^{9,10} induces a diffuse type of injury to the liver which involves all of the epithelial tissue of the liver lobules. Not infrequently this type of injury to the epithelial tissue of the liver as well as that of the kidney is both so severe and diffuse that the chemical and morphological changes of repair cannot be established. Such animals fail to survive. The order of change which uranium induces in the liver depends upon two factors, the age of the animal, and the dosage of this injurious agent. When these variables are properly adjusted either a slight or a severe structural injury may be established in the liver. Such injuries have certain quantitative functional expressions which are not very dependable, especially when they involve the use of some specific test for liver activity. The point of interest now under consideration, however, does not concern itself with quantitative functional expressions of injury. It does concern itself with what these slightly or severely injured cells do, what type of change they undergo during the process of repair. Responding to a slight or moderately severe injury, within eight days such epithelial cells effect a complete process of repair, either by recuperation or cell division with no change in the structure of such cells. The liver returns to its established normal structure. The rapidity with which constructive changes of repair can be effected in this organ is remarkable, and this in turn constitutes one of its factors for safety. If now such an animal be starved for 24 hours and be given chloroform for one hour and a half, this change or repair of the liver structure back to the normal is found not to have imparted any fixed epithelial cell resistance to the liver. These cells which had changed during the process of repair from degenerated types back to a normal order of cell are susceptible to the toxic action of chloroform and become injured, just as they would had the animal not been subjected to the epithelial injury by the use of uranium. If, however, the liver of an animal be more severely injured by uranium, and for this purpose older animals are selected, the outcome is different. In such animals the acute injury to the liver lobules is not only diffuse, but it is more severe than was the case with the former group of animals. In this latter group of animals which survive such a severe in-

toxication, the repair process is of a different type from that arising when a slight epithelial injury is induced. Such severely injured cells are incapable of establishing a state of repair through a process of recuperation without cell division. Furthermore, when changes within such cells have developed which permit and may also inaugurate cell division, the newly formed cells which result from such division are of an abnormal order. In place of being highly specialized in internal structure and polyhedral in form, they are a flattened type of cell and the cell substance frequently fails to show differentiation into cell entities. This changed tissue which results from repair, after an injury is atypical and abnormal in nature for this organ and resembles in some of its characteristics embryonic tissue. It has a functional value though less than that of normal hepatic tissue. It forms bile, stores glycogen, and removes from blood plasma certain dyes which may be used as an index of hepatic function. The observation of interest and significance in connection with this abnormal change in the liver resulting from a repair process is not the return of a satisfactory state of function, but the fact that such changed tissue has acquired a marked resistance to chemicals for which a normal type of cell in this location is highly susceptible. Such flattened, repair cells are resistant to chloroform, alcohol, carbon tetrachloride and uranium. Such an animal may now be starved, not for 24 hours, but for 48 hours, and given chloroform for two and one-half hours in place of one hour and a half without inducing injury or necrosis of the newly formed, functional, atypical cells of repair. A repair process, indicated grossly by a change in form which it is assumed has been associated with a change in the chemical nature of the cell, has led to the development of an acquired resistance to certain chemical agents which are invariably toxic for a normal order of liver cell. This same factor of change continues to operate in these cells which have acquired a transitory resistance. There appears to be a fixity of purpose in cells which manifests itself by a tendency of cell types to reestablish their normal form. The abnormal type of resistant cell which has been described is not fixed nor static in its configuration. After some months it has a tendency to, or actually does, change back to a normal order of highly specialized hepatic epithelium. When such a change in chemical constitution has developed, these cells which have reverted back to the normal have lost their acquired resistance. This normal type of tissue is susceptible to the now injurious, degenerative effect of chloroform, uranium, carbon tetrachloride and alcohol.¹¹

During the years over which these studies on form and changes in form have extended, a large number of senile animals have come under our observation. In a certain percentage of these animals, associated with the development of the senile state, there has occurred a change in the form of epithelial cell which is found in the liver. In such animals the specialized, polyhedral type of cell has been replaced by a flattened, atypical type, identical with that form of cell which may be induced to appear in the liver as a repair process when this organ has been sufficiently injured by some chemical agent. This naturally acquired shift in cell type associated with senility shows the

same order of resistance to chloroform, uranium, alcohol and carbon tetrachloride as is developed by severely injured cells during repair

These changes in cell form as life adjusts and adapts itself to a variety of chemical experiences are impressive as they give to one a conception of the elasticity and adjustability of such changes ever tending to adapt an organ in which they occur and the organism, the individual as a whole, to life at some level of effectiveness. The observations lead one away from a concept of the fixity, the static nature and inelasticity of life processes, even when expressed as chemical equations within cells, as a form of life. It would appear that change is the essence of life and that an organ or organism, with the greater degree of adaptability to changed conditions is in turn the more likely to survive.

Finally and in summary, when we contemplate our varied factors for safety, for a continuation of life as an ever changing, shifting, yet balanced living entity, we may wonder at the brief duration of our life span. The duality of certain organs and the superabundance of reserve tissue in those not so paired, the ability of tissues automatically to throw into operation functional defense mechanisms, degenerative changes in tissues leading to processes of repair which afford tissue resistance, all tend to hold us not only in life, but in a balanced and, in some measure, an effective life.

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CASE REPORTS

PRIMARY TUMOR OF THE INFERIOR VENA CAVA AND HEART WITH HEMOPERICARDIUM AND ALTERNATION OF THE VENTRICULAR COMPLEXES IN THE ELECTROCARDIOGRAM *

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TUMORS of the heart, both primary and metastatic, are usually considered rare Yater¹ summarized most of the literature up to 1931 and in the reports of authors quoted by him, the incidence of metastases to the heart varied from 02 per cent to 14 per cent of all autopsies and from 37 per cent to 75 per cent of all cases with malignancies Scott and Garvin² noted series of cases published by Lymburner, by Pollia and Gogal and by Hellwig in which the incidence of tumors of the heart and pericardium varied from 02 per cent to 09 per cent of all autopsies and from 20 per cent to 60 per cent of all cases with disseminated neoplasms In their own series of 11,100 autopsies, Scott and Garvin found 118 malignancies of the heart and pericardium among 1082 cases with malignant neoplasms elsewhere in the body or an incidence of 109 per cent Our relatively small autopsy series composed of 355 cases examined in the last few years at this hospital included six cases with tumors of the heart and pericardium or a percentage of 17 per cent This incidence is somewhat higher than in most of the larger series and is apparently not related to the number of lung tumors in the autopsied group (535 per cent) because in only one of these cases was cardiac metastasis noted

Primary tumors of the heart, most of which are benign, are much less common than metastatic tumors Hallack, Watson and Berman³ have recently reported a primary tumor of the inferior vena cava and note that only four other such cases have appeared in the literature In one of our cases, the lesion, which was unsuspected before death, proved to be a primary malignancy involving the inferior vena cava, right auricle, right ventricle, and the epicardial surfaces of the aorta and pulmonary artery

A report of this case is presented both because of the rarity of the lesion and because of the unusual clinical manifestations associated with it

CASE REPORT

C N, a 45 year old colored barber, stated that he had been "fine" until his present illness and had never consulted a doctor although during the preceding year he had suffered from a number of vague complaints characterized by bloating, belching, palpitation and nervousness

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About a week before coming to the hospital, the patient developed "cramps" in his legs after sitting on wet grass and shortly thereafter noticed that his legs were swollen. He became very dyspneic so that he could not climb a flight of stairs, and it seemed to him that his heart "dragged down" from the swelling. Oliguria was noted, although previously he had had nocturia two or three times nightly.

He continued to work as a barber until the night before admission when he suddenly felt faint and an hour later while at stool became completely unconscious. The attack was associated with profuse perspiration. After regaining consciousness, he went to bed and the following morning came into the hospital.

The patient was well nourished and well developed but appeared chronically ill. His breathing was rapid and shallow. The neck veins were distended to the angle of the jaw. The cardiac dullness was greatly widened both to the right and left, there was no visible pulsation of the heart. The heart sounds were barely audible and no murmurs could be distinguished. There was an arrhythmia of the heart, the character of which was not determined. Pulsations in the peripheral arteries were very small, and the blood pressure was 98 mm Hg systolic and 78 mm diastolic. No râles were heard on auscultation over the lung bases, although percussion suggested some pleural effusion bilaterally. The liver was palpated three fingers' breadth below the costal margin and there was ascites as manifested by shifting dullness. Edema of the lower extremities was marked.

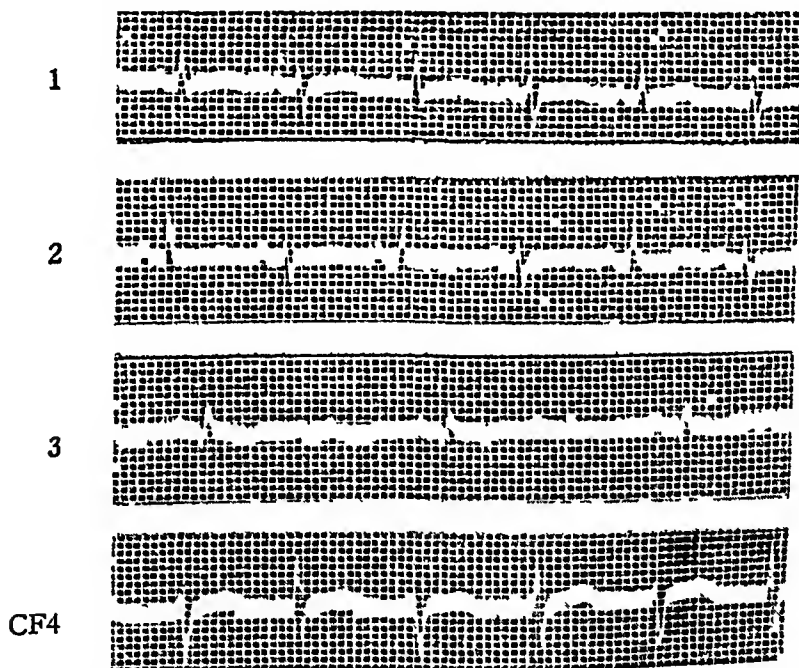


FIG 1 Electrocardiogram taken day after admission to hospital showing alternation in QRS complexes of all leads

An electrocardiogram (figure 1) taken the day after admission showed a sinus tachycardia with alternation in the direction of the QRS complexes in Leads I, II and IV F. In all leads the voltage was low, and in Lead III which was of particularly low voltage the QRS complexes alternated in amplitude rather than direction. There was nothing to indicate that the origin of the impulses varied in any of the complexes.

A roentgenogram of the chest taken on the same day with the patient erect and the tube at six feet showed a globular cardiac shadow greatly exceeding normal dimensions. There was a small amount of fluid in both costophrenic angles. The next day the patient was fluoroscoped in the upright position at which time very little

junctional premature contractions. The alternation (figure 3b) when the rate was intermediate does not appear to be the same as that illustrated in figure 1

The last electrocardiogram obtained from this patient did not show alternation in any form. The voltage was very low and QRS IV F was entirely minus except for a minute primary plus deflection (R)

The day after admission the patient's blood count showed 5,010,000 red cells, 5,300 white blood cells, and 15.5 gm per cent hemoglobin. The non-protein nitrogen was 89 mg per cent, and the blood Wasseimann and Kahn reactions were normal

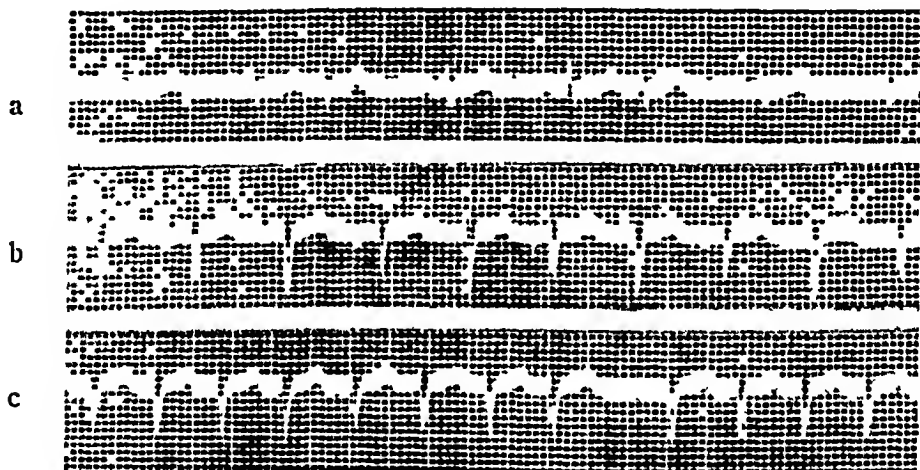


FIG 3 Electrocardiogram taken during successive phases of tachycardia a Lead I b Chest lead with chest electrode placed in third interspace at left sternal border and indifferent electrode on left leg connected so that positivity beneath the chest electrode causes an upward deflection in the electrocardiogram c Same as b during paroxysm of tachycardia

It was agreed that the patient had a pericardial effusion with cardiac tamponade without any of the usual causes to explain it. A paracentesis of the pericardial sac was attempted about 10 days after admission to the hospital. The needle was inserted posteriorly beneath the angle of the left scapula in the ninth intercostal space. Clear straw-colored fluid was obtained from the pleural cavity and upon inserting the needle slightly deeper, blood was obtained. About 20 cc were withdrawn and although there was no definite bumping of the needle, the operator was not sure that he had not entered a cardiac chamber so the procedure was discontinued. The patient made no complaints and exhibited no untoward signs during or immediately following the paracentesis. It was noticed that the blood which had been withdrawn did not evidence any tendency to clot in the 30 minutes or more before it was sent to the laboratory for guinea pig inoculation. Neither the blood nor the pleural fluid produced a tuberculous reaction in guinea pigs.

The patient's condition became progressively worse and he died on July 20, 1939, 25 days after his sudden collapse and about five weeks after the first symptoms of congestive failure.

Autopsy Both pleural spaces contained approximately 1500 cc of clear, amber-colored fluid, the lungs were partially collapsed. No evidence of pulmonary tuberculosis was noted. There was a moderate amount of fluid in the peritoneal cavity, and the liver was not particularly enlarged. It was generally pallid, although thick blood exuded from the cut surface.

The pericardial sac occupied a large part of the thorax. It was tense, bluish black, and contained over 2000 cc of blood. This was not clotted but the red cells had largely settled into the dependent portion of the sac, leaving a syrupy, bile-colored plasma on the surface. The heart was not enlarged, in fact, the muscle substance seemed decreased and the chambers contained no clot. On the anterolateral aspect of

the inferior vena cava, just before opening into the right auricle and within the pericardial sac, there was a bulging mass about 2 by 3 cm in dimension which appeared to be an organized clot. There was a rupture in the wall of the vessel 1.5 cm long which the mass largely occluded. On opening the vena cava this friable, thrombus-like substance extended through the wall of the vessel and involved a somewhat larger area on the inner surface. There was a definite thickening of the caval wall which extended into the auricular wall, forming a crescentic raised ecchymotic area on the endocardial surface. There were other smaller, discrete nodules projecting slightly on the endocardial surface of the auricle and one in the right ventricle beneath the tricuspid valve. Over the pericardial surface of the aorta and pulmonary artery, and particularly in the epicardium between these two structures, there were bleb-like elevations about 1 cm in length which contained soft, bloody material.

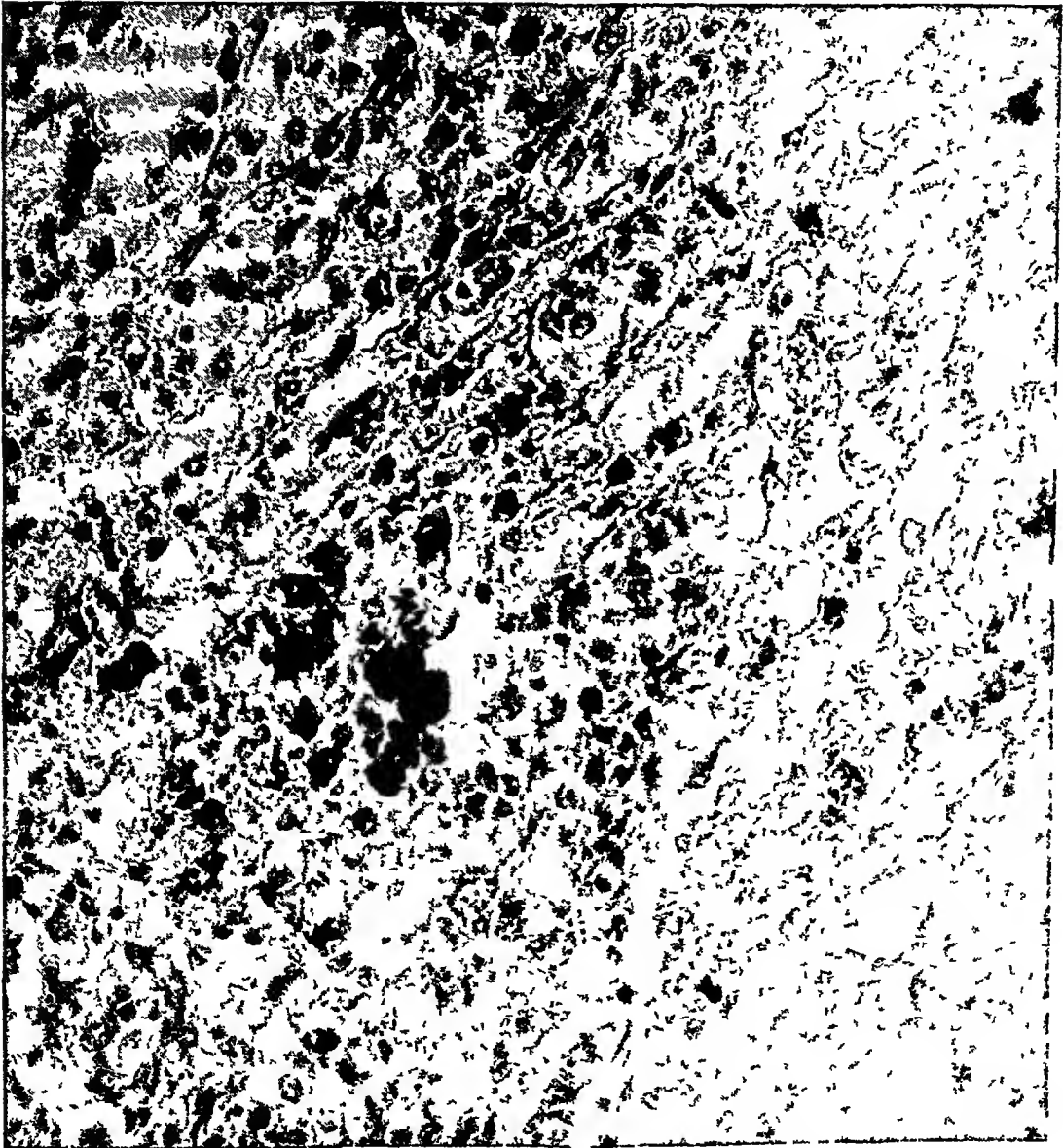


FIG 4 Section through the wall of the inferior vena cava showing structure of the tumor and types of cells present.

The other gross findings in the autopsy were not particularly significant. No tumor was found in any other portion of the body.

Histology A section through the rent in the inferior vena cava (figure 4), including the mass and the adjoining "normal" portion of the inferior vena cava, revealed marked disorganization of the wall due to widespread hemorrhages of different sizes and ages and infiltration by cells of many types.

The background for the infiltrating cells was, for the most part, the spread fibers of the vessel wall and in some places a newly formed, loosely packed connective tissue stroma. Diffusely spread through its meshes were many freshly extravasated red blood cells. Many of the erythrocytes were fused in the process of destruction and an abundance of hemosiderin was seen in phagocytes.

The infiltrating cells were widespread, numerous, rather loosely packed and showed variation in size, shape and staining qualities, but fell into three main groups.

Group 1 One very common cell was rather irregularly elongated, measuring about 12μ by 5μ , with a large, round or oval nucleus containing a pale nuclear sap. One nucleolus and several strands of chromatin were seen regularly. The cytoplasm, seen with difficulty, was rather scanty, stained faintly eosinophilic and contained no granules.

Group 2 Almost as common was a cell roughly polygonal or circular in shape about 12μ in diameter with an eccentrically placed bean-shaped nucleus which was homogeneous and slightly pink staining. The nucleus filled more than half the cell, and its concavity was directed toward the larger cytoplasmic mass which stained lightly neutral and contained no granules.

Group 3 There was a scattering of lymphocytes, polymorphonuclear leukocytes (mature fibroblasts), and an occasional eosinophilic leukocyte.

None of the cells was arranged like a glandular structure or in any other regular manner. Many of the large cells (group 2) had two or three nuclei, but active mitosis was not recognized. There was no fibrosis.

The wall of the right auricle (figure 5) showed the same extensive hemorrhage and invasion by exactly the same sort of cells and in about the same proportion as described for the inferior vena cava. There were several differences, however, apparently due to the dissimilarity in structure of the vena cava and auricle.

(1) No subserous fat was seen, but the epicardial fibrous layer was distinct. The "tumor" extended to this structure but did not penetrate it. One limited area showed raising of the mesothelium by an accumulation of erythrocytes and lymphocytes. No fibrin overlaid the epicardium.

(2) In the myocardium, dying muscle fibers were easily recognized. Some were slightly enlarged, but for the most part they were atrophic and seemed to be dissolving. In areas away from the most active part of the "tumor" the myocardium showed degeneration and atrophy (pressure?) but there was a distinct fibroblastic response here and some fibrosis. In the most active part of the lesion muscle fibers could not be recognized.

(3) The "tumor" invaded the subendocardium, and in localized regions growth was uneven, the endothelium being thrown up into large finger-like projections covering a central core of new growth. In such "villi" lymphocytes were common, but cells of groups 1 and 2 were also seen spread through a loose stroma. Hemorrhage was slight and not very recent. No thrombus was attached to the endocardium.

A section taken through one of the isolated blebs in the adventitia of the pulmonary artery showed an extremely hemorrhagic, circumscribed lesion made up of the same types of cells noted in the caval and right auricular tumors. The lesion was limited to the adventitia, the media being normal except for one area in which a small,

homogeneous, hyaline, acellular zone of necrosis was seen. In the adventitia, however, the tumor had led to the destruction of the periarterial nerves and obliteration of many of the vasa vasorum (which may explain the zone of medial necrosis). The intima showed no abnormalities and the endothelium was intact.

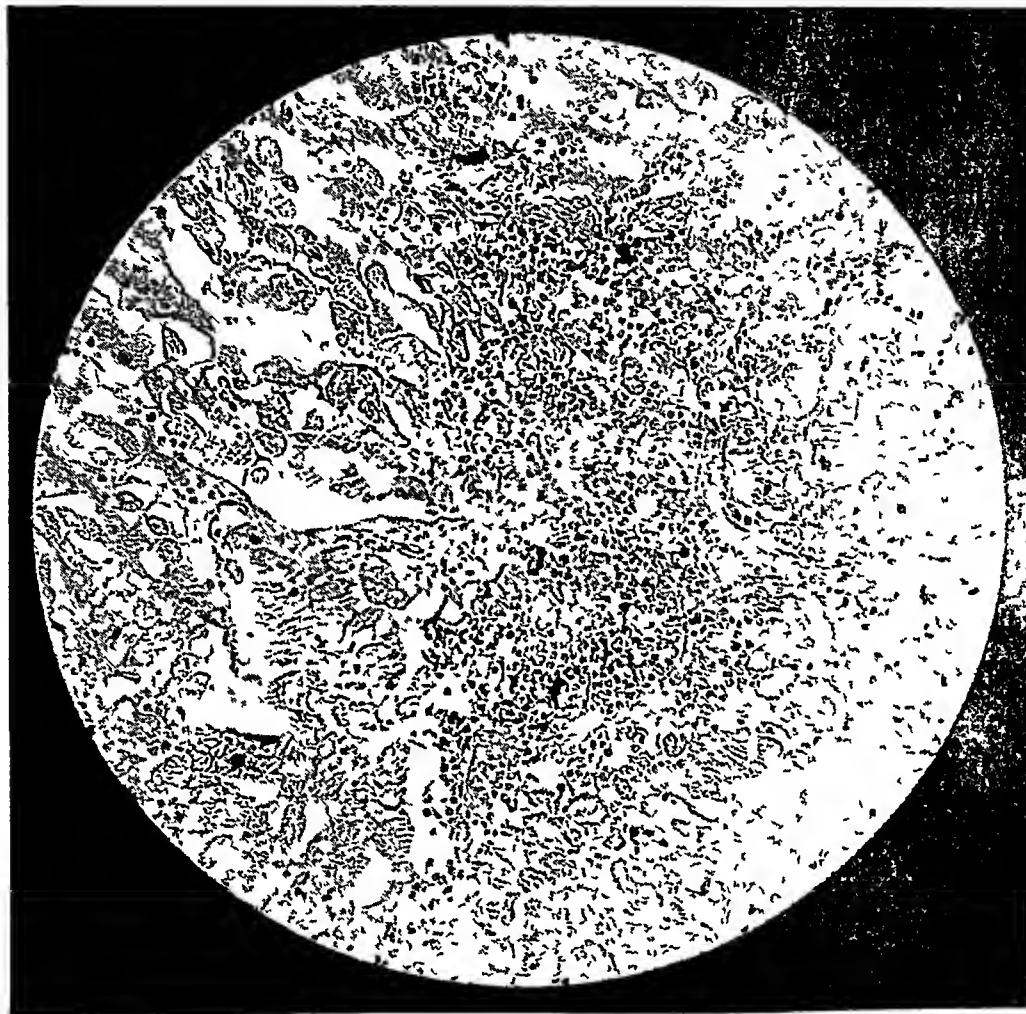


FIG 5 Section through wall of right auricle showing invasion of the myocardium by the tumor

A section through an apparently normal portion of the left ventricular wall at the base of the heart showed a considerable submesothelial infiltration of the subserous fat by hemosiderin laden phagocytes and many small lymphocytes. No tumor cells were seen. Except for early changes of sarcolytic degeneration and some infiltration of the interstitial spaces of the myocardium by mononuclear eosinophiles and fibroblasts, the heart muscle was normal. The endocardium was intact throughout.

The nature of this lesion of the inferior vena cava and right auricle is uncertain. It has been suggested by those who have examined the sections that the lesion might represent chronic inflammatory reaction, sarcoma or endothelioma. The difficulty in distinguishing among these three is recognized by Ewing⁴ who

in his discussion of endothelioma, states that "Vascular endothelium also proliferates readily in inflammation and forms collections of cells which may resemble the groups of endothelioma or carcinoma," and again, "The studies of recent years have served chiefly to emphasize the difficulty of separating true endothelioma from many typical sarcomas, lymphosarcomas, carcinomas and certain embryonal tumors"

We are inclined to believe that the lesion in our case is an endothelioma because of (1) the origin of the tumor in the wall of a blood vessel, (2) the rather primitive, mesenchymal appearance of the cells; (3) the multiplicity of the lesions—discrete nodules were found in the inferior vena cava, right auricle, right ventricle and adventitia of the aorta and pulmonary artery, (4) the low grade invasiveness of the tumor.

COMMENT

Tumors of the heart, even when of great size, often produce no functional disorders, a fact which precludes an estimate as to how long the neoplasm had been developing in our patient. It is quite probable that the onset of symptoms corresponded with the rupture of the vena cava resulting in cardiac tamponade from the hemopericardium. Hemorrhage into the pericardium occurs occasionally in dissecting aneurysm and myocardial infarction as a terminal event, but survival for any prolonged period of time is unusual. Our patient lived about five weeks after the onset of symptoms and during part of this time he was ambulatory. Rixford⁵ described a case in which the patient lived about nine weeks following trauma that caused rupture of the right auricle with hemopericardium. McNamara⁶ reported a case with metastatic carcinoma of the auricle which ruptured. This patient had an accentuation of his cardiac symptoms 17 days before death, presumably at the time of rupture. The duration of survival must depend largely upon the underlying pathology in the heart and the rapidity with which blood is lost from the circulation, which also governs the degree of tamponade. In most instances, except when the hemopericardium is due to trauma, the duration of survival may be largely of academic interest, but the possibility that intrapericardial rupture may not be immediately fatal must be considered in diagnosis. The relatively low pressure in the vena cava and the partial obstruction of the rupture by thrombus formation probably accounts for the prolonged course in our case.

Another unusual feature was the alternation of the QRS complexes in the electrocardiogram during a part of this patient's illness. It has already been noted that there was at different times an alternation both in the direction and shape of the QRS complexes and also in their amplitude. The alternation in amplitude illustrated in figure 3b is probably due to regularly recurring impulses arising in the junctional tissues alternating with impulses from the sino-auricular node. Although the QRS complexes with the highest amplitude were not regularly preceded by distinguishable P-waves, these complexes did not always occur prematurely and were not always followed by longer R-R intervals as might be expected with premature contractions.

As contrasted with this alternans the type exhibited in figure 1 occurs in a regular sinus rhythm, the direction of the principal deflections in alternating complexes being exactly opposite except in Lead III where the amplitude is low.

Brody and Rossman⁷ state that differentiation should be made between electrical alternans and bidirectional complexes which our case seems to show. It differs from the case presented by Smith⁸ to which they refer, however, in that the rhythm is of sinus origin rather than an ectopic ventricular rhythm and the R-R intervals are constant. Hamburger, Katz and Saphir⁹ quote Kisch¹⁰ to the effect that electrical alternans may consist of variations in either the amplitude, contour, duration or direction of the involved complexes. In this sense the electrocardiogram reproduced in figure 1 can be considered an example of electrical alternans.

Electrical alternation is generally considered an expression of the mechanical behavior of the ventricles and may, therefore, be associated with a pulsus alternans. We did not observe this phenomenon in our patient but cannot be sure it was not present. The usual view concerning mechanical alternation is that the weak beat is weak because fewer muscle fibers contract. Lewis¹¹ suggests that in alternation all regions of the muscle contain defective fibers, the concentration of which is greater in some regions than another, thus, under certain circumstances the defective fibers might participate in the contraction of the ventricle only on alternate beats. He thinks that "The order in which muscle elements are activated would not be disturbed in these circumstances," and in his experience "The change and variations in the electrocardiographic curves of axial leads are too small to be compatible with the failure of relatively large and solid masses of ventricular substance." The shape of the complexes in our case, however, suggests an alternating pathway for the ventricular wave of excitation or an alternating relationship of the heart in space to good conductors. Brody and Rossman⁷ also suggest that "alternation may be due either to two alternating foci of impulse formation or to two alternating paths of conduction from one focus." A more gradual phasic variation of the electrocardiogram may occur normally with respiration, and Hamburger et al.⁹ noted slightly alternation for one to three cycles related to inspiration in one of their cases. To produce the regular alternation at the rapid heart rate noted in our case would presumably have required a very rapid respiratory rate which the patient did not exhibit, although graphic records of respiration were not obtained.

All authors agree that alternation is observed only when "The muscle is laboring and in difficulty" and that it indicates a very unfavorable prognosis. Experimentally¹¹ it has been produced by increasing the cardiac rate, by administering various poisons such as digitalis, aconite, glyoxylic acid and hemolytic serum, and also by occluding a coronary artery. Clinically, coronary arteriosclerotic heart disease is most often the underlying disease when alternans is noted. Our patient presented no unusual damage of the coronary arteries or the ventricular myocardium. The large hemopericardium with tamponade undoubtedly did interfere with myocardial nutrition and may have been responsible for the transient alternans noted in the electrocardiogram. Feldman¹² reported a case with serosanguinous pericardial effusion from carcinomatous metastasis in which alternans was observed in an electrocardiogram obtained shortly before death. He assumed that the electrocardiographic abnormalities were due to myocardial changes resulting from interference with the coronary circulation by the tamponade. Harvey and Whitehill¹³ also noted "alteration in amplitude was occasionally observed as was change in the form of each second or third complex" in tuberculous pericarditis with effusion.

It is to be noted that alternation was only a transient phenomenon in our case, a characteristic usually noted by others. This was true in spite of the persistence of the tamponade and, therefore, the disappearance of the electrical alternans did not indicate an improvement in the heart muscle but perhaps a more generalized depression of all the muscle fibers so that their function was equally poor. Although the location of the lesions in the right auricle suggests the possibility of aberrant excitation waves and the unclotted blood in the pericardium might have alternately affected conduction from the heart, the best explanation for the electrical alternation probably is that it depends upon functional myocardial changes resulting from coronary insufficiency.

SUMMARY

A case is presented in which rupture of the inferior vena cava with hemo-pericardium occurred. This rupture traversed a lesion in the wall of the vena cava which in our opinion was an endothelioma. Similar growths were found in the wall of the right auricle, right ventricle and the epicardial surfaces of the aorta and pulmonary artery. The patient survived the rupture of the inferior vena cava for at least 25 days, and during the course of his illness the electrocardiogram exhibited electrical alternans on several occasions.

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HYPERPARATHYROIDISM WITH CALCINOSIS AND SECONDARY TO RENAL DISEASE, REPORT OF A PROBABLE CASE*

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HYPERPARATHYROIDISM^{1,2,3} is usually due to an adenoma of one or more of the parathyroid glands, but occasionally it may be due to diffuse hypertrophy (hyperplasia?) † of all parathyroid tissue^{4,5}. The adenomata⁶ may be composed of one dominant cell type or of a mixture of cell types, but the hypertrophic glands are uniformly composed of large cells with clear cytoplasm, the so-called large ‡ "wasserhelle" cells. The distinction, however, is purely on the basis of the anatomical alterations in the parathyroid glands since the resultant disease is similar. Renal complications are common⁷. For example, in a survey of 83 patients with hyperparathyroidism, Albright, Baird, Cope and Bloomberg⁸ found 23 with renal lithiasis, one with acute renal insufficiency, and 19 with calcium precipitation in renal tubules with resulting renal sclerosis, contraction and insufficiency.

The above relationship, primary parathyroid disease followed by renal alterations, is well known. The reverse of the sequence of events, primary renal disease followed by secondary (compensatory?) hyperplasia of all parathyroid tissue is also well recognized⁷. Although the exact mechanism is not known, there is experimental evidence to show that the parathyroid hyperplasia is secondary to the renal disease⁹. It is probable that the degree of parathyroid hyperplasia is roughly proportional to the length of time renal insufficiency has been present^{9,10,11} and that excessive enlargement, often accompanied by alterations in the bones, is most probably the result of severe renal insufficiency of long duration¹¹. As Albright, Drake and Sulkowitch suggest,¹¹ the fact that renal insufficiency does not usually last for a long time probably explains why marked secondary parathyroid enlargement is not common.

The anatomical alterations of the parathyroid glands in secondary hyperplasia are reviewed by Castleman and Mallory¹⁰ who suggest exact criteria for the diagnosis of the condition. They find that all of the glands show varying degrees of gross enlargement, that they are composed principally of normal sized chief cells, that the oxyphil cells are always greatly increased in number, and that a few small water-clear (wasserhelle) cells are occasionally present. It should be added, however, that the parathyroid hyperplasia secondary to renal disease does not seem to differ qualitatively from that present in a variety of other conditions¹⁰. Furthermore, Castleman and Mallory¹⁰ state "It is remotely possible that localized, adenoma-like hyperplasia is occasionally the response of the parathyroid glands in secondary hyperplasia."

From available data, as Albright, Drake and Sulkowitch¹¹ suggest, it appears that the following three conditions occur (1) primary hyperparathy-

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† For a discussion of hypertrophy vs hyperplasia see reference 5.

‡ In contradistinction to small "wasserhelle" cells seen in secondary hyperplasia, as will be noted later.

roidism due to adenoma and predisposing the patient to renal disease; (2) primary hyperparathyroidism due to idiopathic parathyroid hypertrophy (hyperplasia?) and, likewise, predisposing the patient to renal disease; and (3), primary renal disease which, if it is severe and of long duration, may lead to parathyroid hyperplasia and, occasionally, to osteitis fibrosa generalisata

Recently Albright, Drake and Sulkowitch¹¹ described an apparently rare syndrome which they named renal osteitis fibrosa cystica. The outstanding features of the syndrome are marked renal insufficiency that has lasted for a long time, phosphate retention in the blood with a high blood serum inorganic phosphorus level, slight reduction of the blood serum calcium level, marked acidosis,

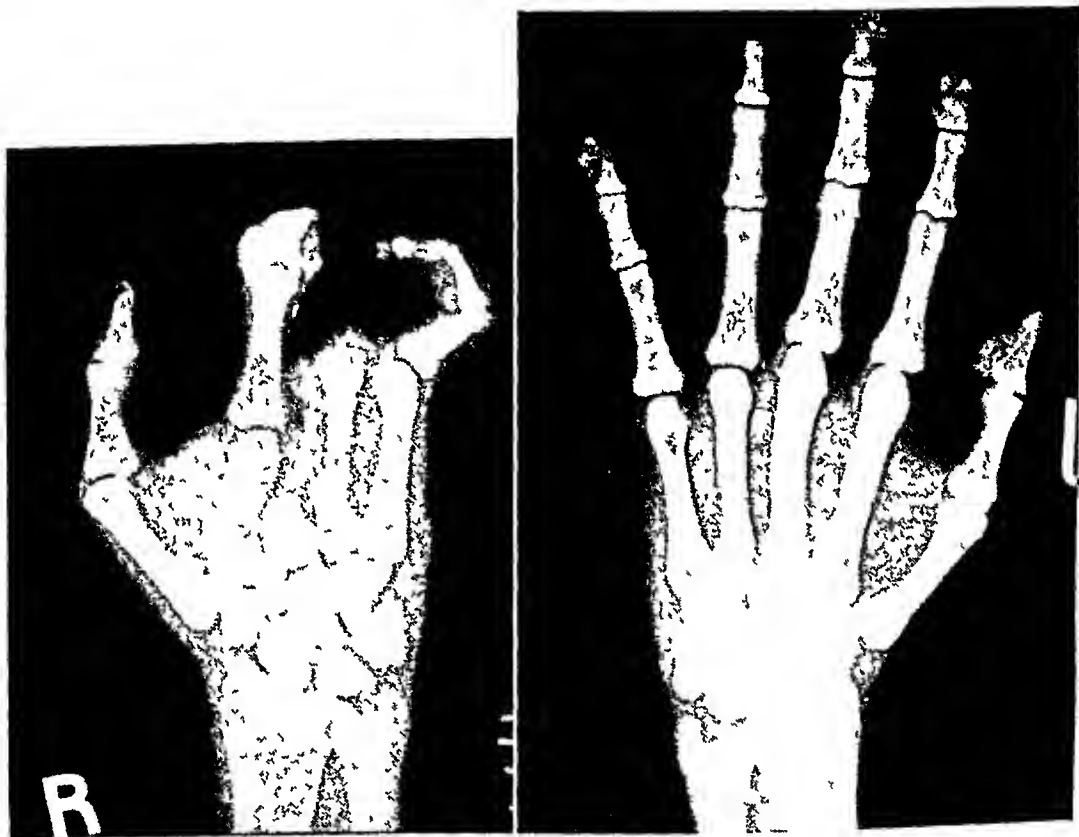


FIG 1 Roentgenograms of the hands

calcium deposits in the neighborhood of joints, extreme calcification of the media of arteries (Monckeberg type), osteitis fibrosa generalisata of all bones, and enormous enlargement of all parathyroid tissue. Their patient had renal disease for 23 years, there was severe renal insufficiency, the serum calcium was 8.2 mg per cent and the serum inorganic phosphorus 9.8 mg per cent, and roentgenograms revealed definite osteitis fibrosa generalisata and many areas of calcium deposition about joints. At necropsy all four parathyroid glands were tremendously enlarged and consisted essentially of chief cells. The authors believe that the condition is the adult counterpart of renal rickets in children, that the renal insufficiency is primary, and that the other features are secondary, the prime requisite being that the renal insufficiency be present for a long time. The parathyroid hyperplasia is believed to be secondary to the phosphate retention occasioned by the renal insufficiency. The osteitis fibrosa may be a

result of the excess of parathyroid hormone but, in the opinion of these authors, a more likely explanation for the pathogenesis of the bone changes is a lack or decrease of calcium absorption from the intestinal tract with a slightly increased resorption of bone due to the acidosis. Calcium balance determinations performed upon their patient are cited to support this latter contention. The explanation for the deposition of calcium around the joints, the feature of the disease which makes it unique, is not clear, but it is suggested that it might be due to the presence of an excess of colloidal calcium phosphate which is quickly removed from the blood. Briefly stated, renal osteitis fibrosa cystica appears to be an extreme and unusual example of parathyroid disease occurring secondary to renal disease (group 3 as discussed above), the outstanding feature being the curious deposition of calcium about the joints.

We wish to report a patient who presented the necessary clinical criteria for a diagnosis of renal osteitis fibrosa cystica, or secondary hyperparathyroidism, but who, in the final analysis, could have had quite the opposite condition, namely, primary parathyroid disease. A difficult and practical problem in differential diagnosis is the result.

CASE REPORT

W O, a white male, aged 40, entered the University Hospital on July 14, 1938. He complained of distress in the region of the joints, abdominal discomfort, headaches, "abscesses" of the finger tips, a mass on the right side of the face, generalized pruritus, and nocturnal diuresis. His history revealed that he had suffered from

CHART I
Blood Chemical Data

Date	Urea N mg %	Creatinine mg %	Plasma Proteins (gm /100 c c)					Plasma Chlorides mg /100 c c
			Date	Fib	Alb	Glob	Total	
7/14/38	95.2	6.6	7/14/38	—	3.08	3.17	—	638
7/17/38	91.0	7.4	7/17/38	51	3.17	2.57	6.25	575
7/24/38	96.6	8.6	10/11/38	81	2.72	2.82	6.35	
8/1/38	96.6	10.9						
8/8/38	92.4	8.4						
8/16/38	84.0	6.7						
8/23/38	86.1	6.7						
8/30/38	88.2	7.5						
9/13/38	88.9	7.1						
10/3/38	130.2	10.5						
10/5/38	145.6	8.4						
10/7/38	130.9	7.8						
10/11/38	139.3	8.5						
10/14/38	105.0	8.3						
			Date	Serum Calcium mg %	Serum Phosphorus mg %	Phosphatase (Bodinsky units)	Alk. Res	
			8/30/38	11.1	7.7			
			9/13/38				45 c c	
			9/15/38	10.9	10.2	14.4		
			10/3/38				43 c c	
			10/5/38				49 c c	
			10/7/38				58 c c	
			10/11/38	12.2	10.0	10.8		
			10/14/38				33 c c	

vague abdominal distress and flatulence for 16 years. In 1926 the right knee became enlarged, hot, tender and very painful for four days, but he was able to resume work in 10 days. During the six year period prior to the time he came to the hospital he noted, intermittently, sharp, shooting pain over the kidney regions when stooping. Blurring of vision had been present for three years. Soon thereafter his physician found pus and albumin in the urine. The albuminuria persisted. In the fall of 1937

he became very weak. In May 1938, following exposure in the rain, he developed an acute delirium and thereafter his finger tips became enlarged and tender, a mass appeared just anterior to the right ear, and generalized pruritus began. In June, 1938, headaches appeared, the knee joints became painful, and there was a marked increase in weakness and fatigability. About one week before he came to the hospital the shoulder joints became painful and nocturnal diuresis, which had averaged four or five times for several months, increased to eight or nine times.

He appeared chronically ill and pale. Scattered over the entire body, but most pronounced on the exposed surfaces were many brownish-black pigmented areas

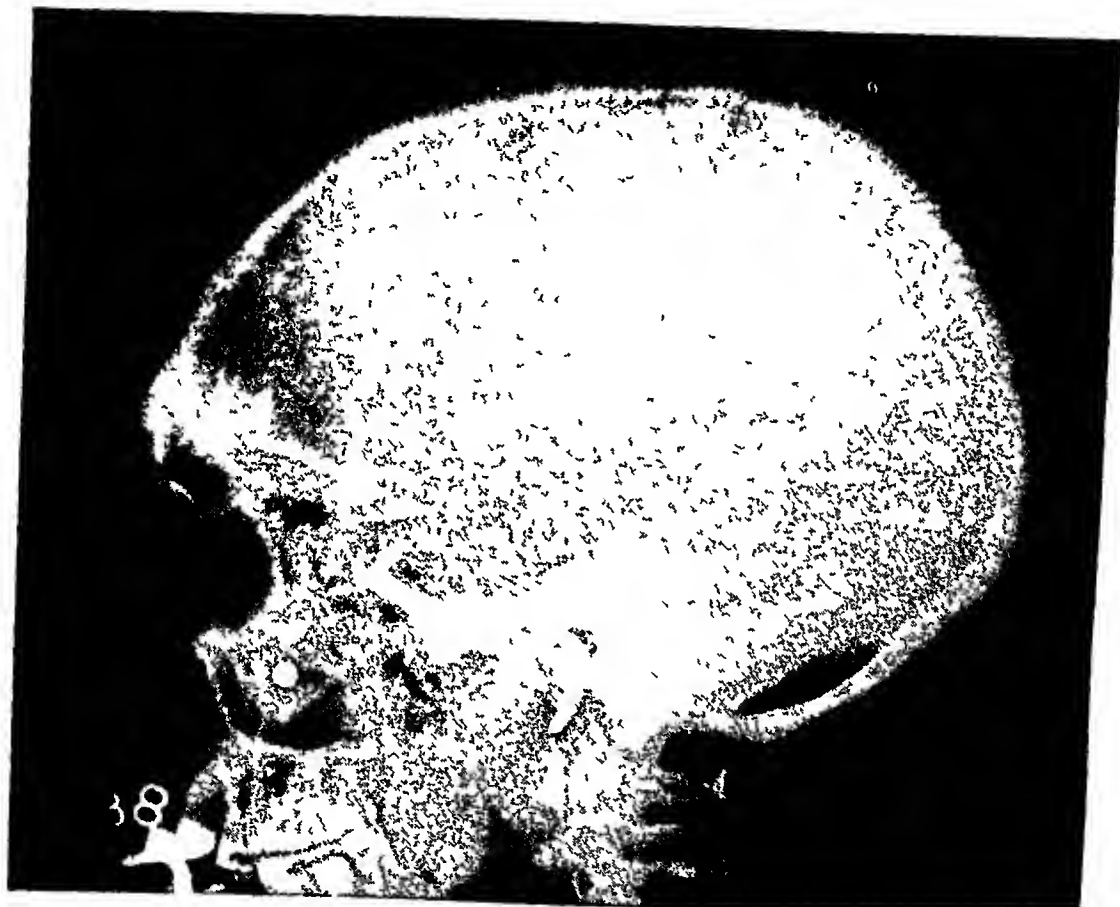


FIG 2 Roentgenogram of the skull

ch were, on the average, $1\frac{1}{2}$ mm in diameter. Examination of the ocular fundi revealed slight, generalized diminution in the caliber of the arteries and the absence of hemorrhages or exudates. A firm, rounded, smooth mass, measuring 3 by 3 by 1 cm, was present just anterior to the right ear. It was only slightly tender, it was fixed to the skin, and it was not adherent to the underlying bone. There was no thyroidopathy. The thyroid gland was not palpable and no masses could be palpated in that region. The extensibility, volume, and density of the lungs were normal. The left ventricle of the heart was moderately enlarged and the arterial blood pressure was 145 mm Hg systolic and 95 mm diastolic. The peripheral arteries were not tortuous but their walls were definitely thickened. No masses or solid organs were palpable in the abdomen. The prostate gland was moderately enlarged. The second and third fingers of the right hand were absent, the result of an accident early in life. There was a bulbous, firm but fluctuant swelling of the second joint of the right index finger. A similar mass was present over the dorsum of the right hand. The right

little finger, the left thumb, and the left index, middle, and little fingers presented bulbous, firm, and slightly tender swellings of the terminal phalanges. The toes were normal. The neurological examination revealed no abnormalities.

The urine consistently had a low specific gravity which varied between 1.001 and 1.013, was alkaline to the litmus paper test, and contained 5 to 6 grams of protein.



FIG 3 Roentgenogram of the pelvis

per liter by the Esbach method. No red blood cells nor hemoglobin were detected in the urine, but a few granular casts and white blood cells were usually present.

The blood contained 5.11 grams of hemoglobin per 100 cc (Newcomer) and 1.0 million red blood cells and 5,350 white blood cells per cubic mm. Of the latter, 73 per cent were neutrophils, 1 per cent eosinophiles, and 26 per cent lymphocytes. The blood Wassermann test was negative. The results of the various blood chemical determinations are shown in chart 1. As will be noted, there was marked azotemia and, although the serum inorganic phosphorus was greatly increased in amount, there was approximately a normal concentration of serum calcium.

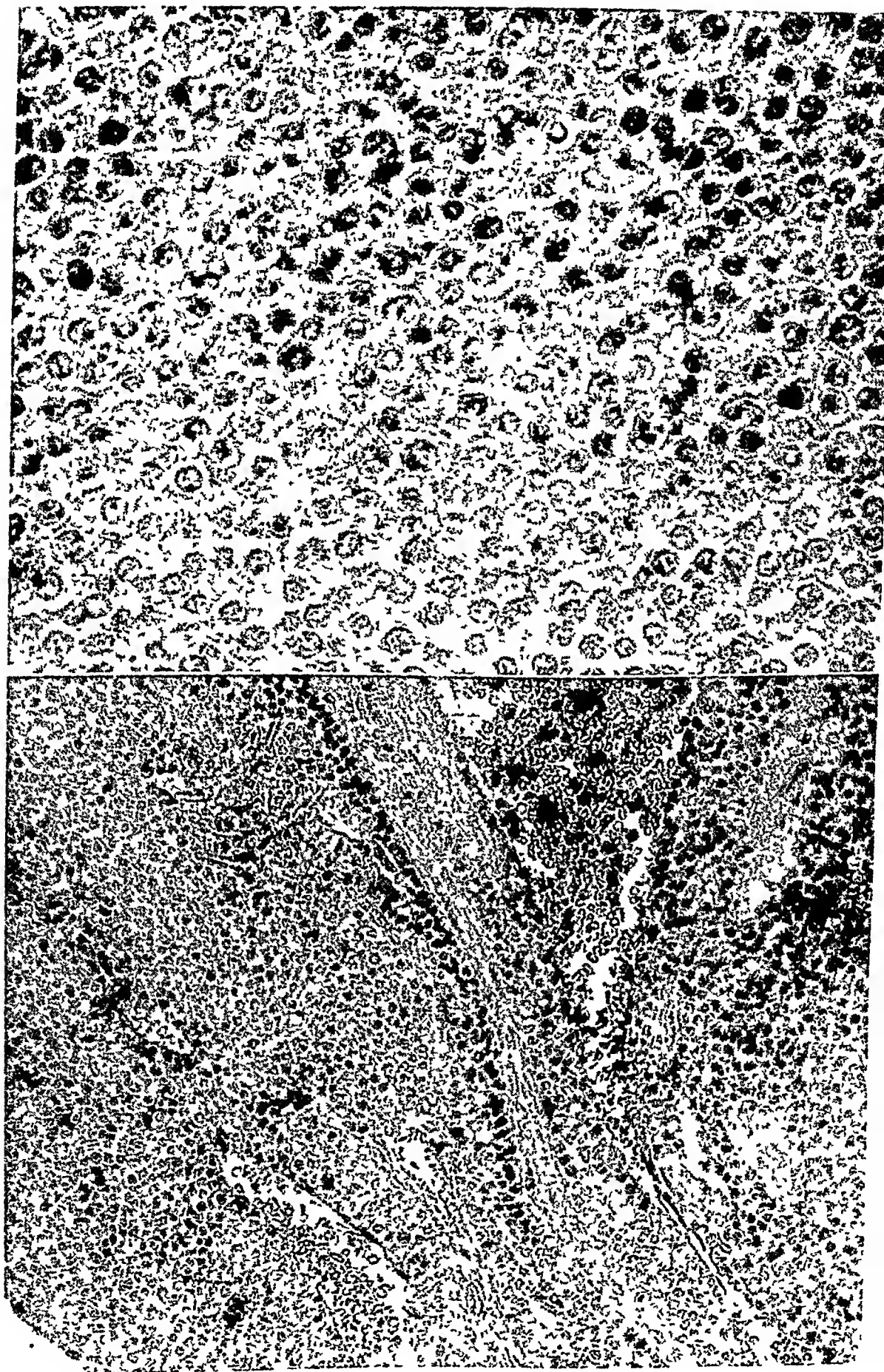


FIG 4 Sections of the parathyroid

Calcium and phosphorus balance studies were not satisfactory owing to the inability of the patient to cooperate. However, in the 24 hour test period, immediately following a 48 hour interval during which the patient ingested a diet of low calcium and phosphorus content, the patient ingested no more than 589 mg of calcium and 1003 mg of phosphorus and excreted 172 mg of calcium and 802 mg of phosphorus in the urine. Roentgenograms (figures 1, 2 and 3) of the skull, pelvis, spine, long bones and hands revealed a generalized osteoporosis but no evidence of cyst formation. The skull had a diffuse, granular appearance with innumerable areas of

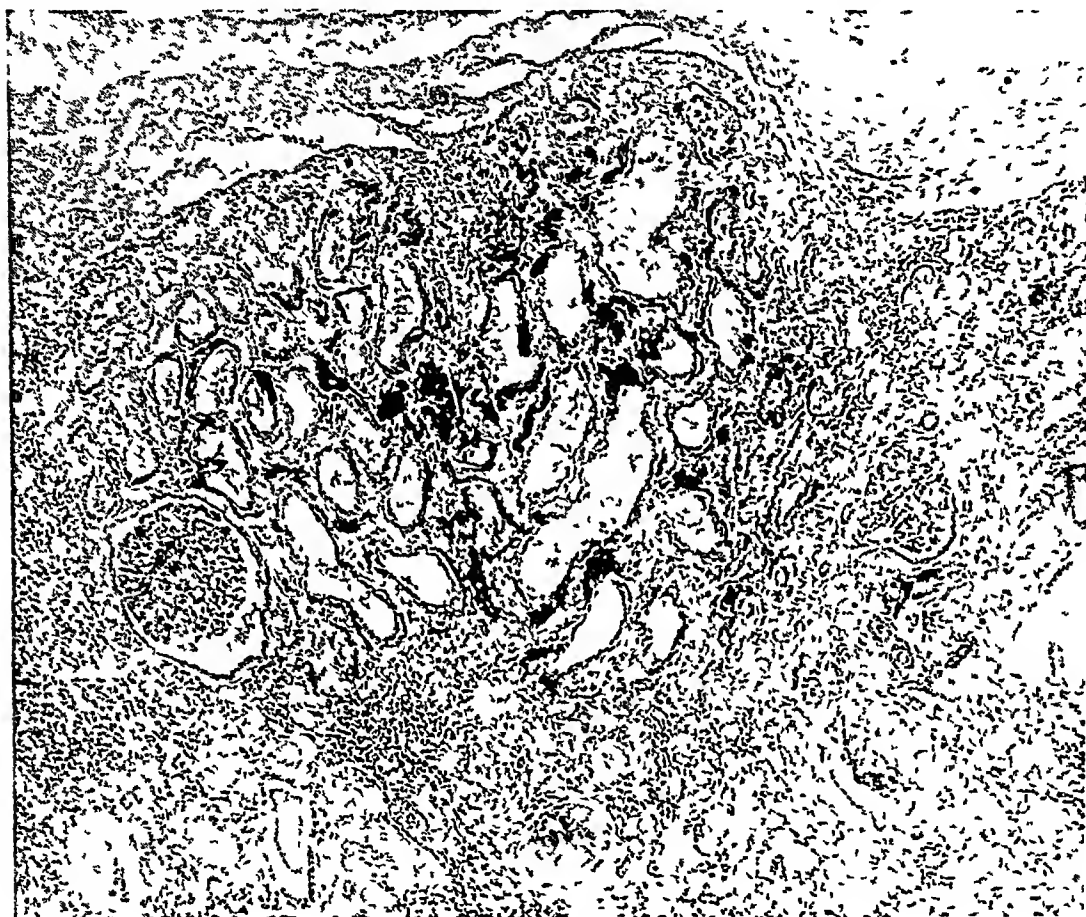


FIG 5 Section of the kidney

lessened density. There were localized areas of calcium density in the soft tissues of the terminal phalanx of all fingers and the thumb of the left hand, about the middle joint of the right index finger, and in the tip of the right little finger. There were similar shadows in the regions of the right elbow, right shoulder, and right hip joints. Roentgenograms of the chest, kidney regions, and the mandible to include the mass mentioned above revealed no extraneous shadows of calcium density.

On September 15, 1938, the mass on the tip of the left index finger was incised and a small amount of milky, thick, white fluid was obtained. No calcified nor solid material was present. On September 17, 1938 similar material was aspirated from the bulbous mass about the second joint of the right index finger. Chemical analysis of the fluid showed that it contained 62.55 per cent water and 28.24 per cent tricalcium

phosphate, 7.79 per cent was insoluble in acid and was thought to be protein, and 1.39 per cent was not identified

The patient died on October 15, 1938. During the 93 day period of observation, nausea, weakness, and generalized pains were progressive. The clinical diagnosis was renal osteitis fibrosa cystica, or hyperparathyroidism secondary to renal disease.

Postmortem examination revealed marked overgrowth of one parathyroid gland,* very small kidneys, generalized osteitis fibrosa, multiple areas of calcification in various organs, generalized arteriosclerosis, coronary arteriosclerosis, myocardial

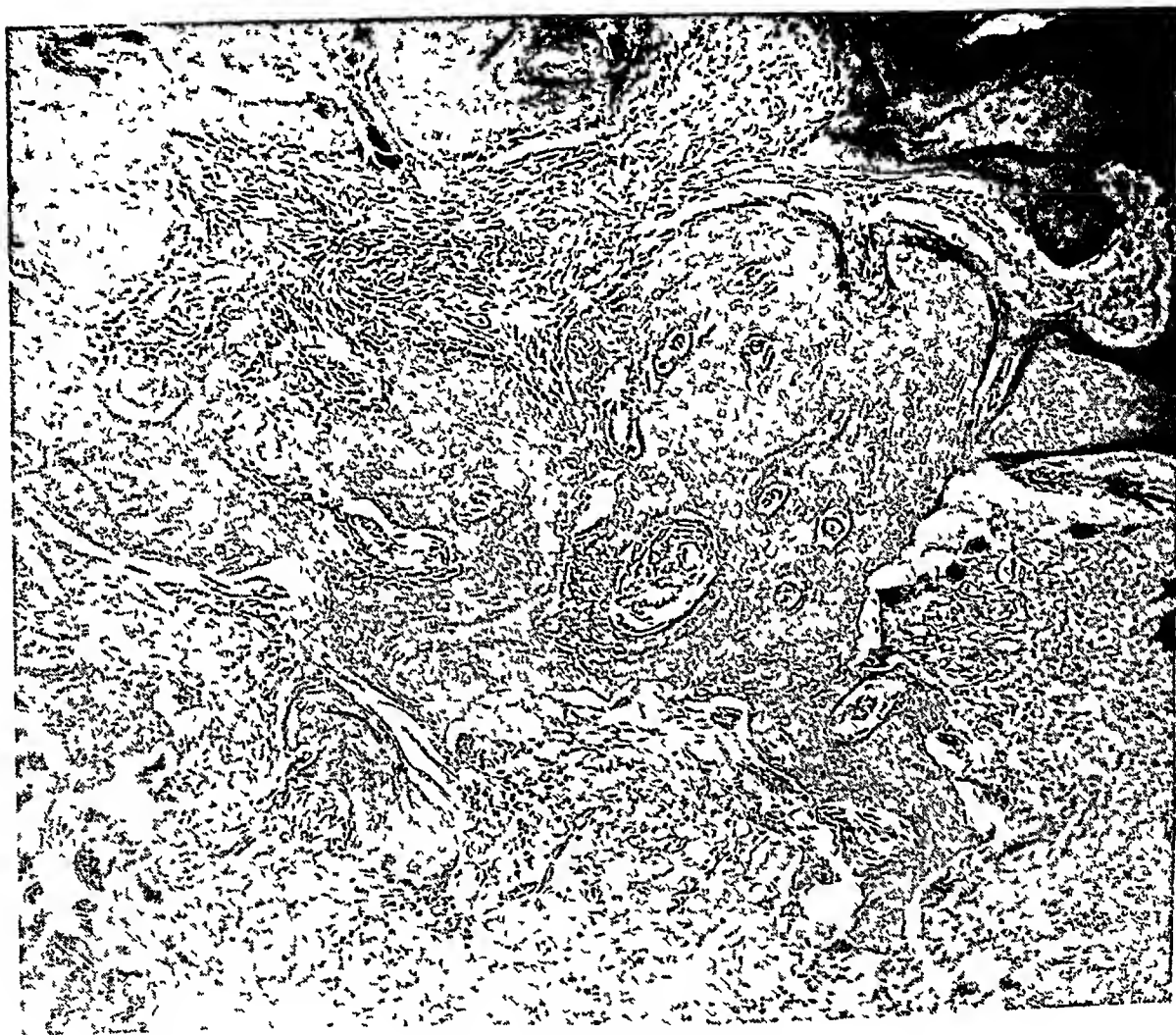


FIG 6 Section of the skull

scarring, cardiac hypertrophy and dilatation, lobular pneumonia, passive congestion of the liver, chronic cystitis, hyperplasia of the prostate gland, multiple cysts of the capsule of the spleen, and a cyst of the brain. Examination of the mass anterior to the right ear and of the hands was not permitted. Pertinent gross and microscopic observations follow.

The parathyroid gland measured 5 by 2½ by 2 cm and contained an area of cystic degeneration in the center. It was composed of masses of closely packed cells separated by wide bands of connective tissue (figure 4). The nuclei occupied the

* A careful search in the neighborhood of the thyroid gland, in the thyroid capsule, and in the upper mediastinum revealed two small masses which were thought to be the other parathyroid glands but were later found to be normal lymph glands.

greater portion of the cells, varied moderately in size, and contained a fine chromatin network, one or more dark blotches of chromatin, and a nucleolus. The cytoplasm of most cells was pale and vesicular but was definitely pink in others. There were numerous blood sinuses around which the cells were lined up in a single row resembling epithelial cells. We believe that the cells anatomically are midway between chief and "wasserhelle" in type. A few scattered, small "wasserhelle" cells were seen but no oxyphil cells could be found.

Each kidney weighed 108 grams and was pale and firm. The capsule stripped away with great difficulty. A cut section revealed the absence of architectural pattern and in many areas it was difficult to detect a line of demarcation between the pyramids and cortex. The cortex was only 3 mm in thickness. The renal pelvis and ureters were normal. Sections of the kidneys (figure 5) showed the surfaces to be pitted and the capsules to be thickened and hyalinized. The glomeruli were greatly reduced in number and were surrounded by atrophic and widely dilated tubules. Collections of glomeruli and tubules were separated from each other by wide areas of scar tissue in which there was evidence of chronic inflammation. There was increased vascularity but the vessel walls were not greatly thickened. Diffuse areas of calcification were conspicuous and numerous throughout the interstitial tissue. Many glomeruli were hyalinized and several showed adhesions between the tuft and capsule. One crescent formation was seen. Many tubules were greatly dilated and some of them contained colloid-like material. A few tubular epithelial cells contained brown pigment and a great many of them contained calcium. The deposits of calcium were very conspicuous both in and about the tubular epithelium and in the interstitial tissue.

The bones of the skull were markedly thickened and the two tables were widely separated by a spongy, reddish-gray, granular tissue. The cortex of the femora and clavicles was normal in appearance. The acromioclavicular joints were very loose owing to the softening of adjacent bone. Sections from the skull (figure 6), clavicles, vertebrae and femora revealed extensive areas of fibrosis between the spicules of bone many osteoblasts, and numerous osteoclasts. No cysts were seen.

Areas of calcium deposition were prominent in the lungs, brain, pancreas, pineal body, and splenic artery. Arteriosclerosis was moderate but definite.

The cyst of the brain was small, surrounded by edema, and had no definite lining.

DISCUSSION

We base our diagnosis of primary renal disease and secondary hyperparathyroidism on severe renal insufficiency, probably of long duration in view of the history of albuminuria and pain in the loins, increased serum inorganic phosphorus, normal serum calcium, acidosis, calcium deposits about the joints, sclerosis of the peripheral arteries, widespread osteitis fibrosa. As noted above, these features also fulfill the requirements for a clinical diagnosis of renal osteitis fibrosa cystica. Dr. Fuller Albright of the Massachusetts General Hospital, Boston, has reviewed the case and agrees with our diagnosis.

In view of the fact that only one parathyroid gland was found we cannot successfully contradict anyone who wishes to call this a case of primary hyperparathyroidism or one of coincidental primary hyperparathyroidism and chronic nephritis. Identification of the parathyroid lesion as that of secondary hyperplasia or that of neoplasia (adenoma) would be decisive but the histological pattern of the gland is not sufficiently characteristic^{6, 10} to warrant an unequivocal decision.

As Castleman and Mallory¹⁰ intimate and this case demonstrates, primary hyperparathyroidism resulting in renal damage and primary renal disease resulting in hyperparathyroidism may so closely resemble each other in their respective end stages as to be indistinguishable either clinically or at postmortem examination. As a rule, in the former condition one finds enlargement of only one parathyroid gland unless the disease is due to hypertrophy, in which case the diagnosis is clear from the parathyroid histology whereas, in the latter condition, one would expect enlargement of all four parathyroid glands. The differential diagnosis in our case is difficult because only one gland was found.

SUMMARY

A case of probable hyperparathyroidism with calcinosis and secondary to chronic renal disease is reported. Certain difficulties in the differential diagnosis between this condition and primary hyperparathyroidism with severe renal damage are pointed out.

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REPORT OF A CASE OF BENIGN GASTRIC POLYP PRODUCING A GASTROGENIC DIARRHEA *

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BENIGN tumors of the stomach constitute a relatively small portion of gastric lesions. According to the figures of Eusterman and Balfour they represent only 0.6 per cent of all gastric lesions seen at the Mayo Clinic. Mayo Clinic statistics show that the average age of occurrence of benign gastric lesions is 46. Twenty-six per cent occur in the body of the stomach and 69 per cent occur in the pyloric or prepyloric regions. Benign gastric lesions include leiomyomata, fibromata, lipomata, hemangiomata and adenomata. The leiomyoma is the most frequent benign gastric lesion and thus usually is polypoid in structure and resembles somewhat submucous fibroid as seen in the uterus. The adenomata are usually multiple.

The most common symptoms of benign lesions in the stomach include dyspepsia, diarrhea, anemia and hematemesis. Nausea and vomiting may occur but are uncommon. The diagnosis is not easy. At the Mayo Clinic a roentgenologic diagnosis was made in 92.6 per cent of the cases. The diagnosis of a benign gastric lesion can hardly be made clinically. The rarity of the lesion and the vague, variable symptomatology are the chief obstacles to clinical diagnosis. Probably the combination of roentgenologic studies and gastroscopic examination followed by surgical exploration is the most accurate and logical method of establishing a diagnosis.

With careful fluoroscopic examination the percentage of correct roentgenologic diagnoses should be high. This is particularly true of pedunculated growths. These are usually freely movable in the lumen of the stomach, and the pedicle is quite easily distinguishable. There is absence of infiltration or rigidity of the surrounding gastric wall, and the growth itself does not usually show areas of ulceration as seen in malignant lesions. In benign growths involving the wall of the stomach, which are not pedunculated, the diagnosis is extremely difficult and unreliable and usually a roentgenologic diagnosis of a malignant lesion is made. Fortunately, however, the greater percentage of benign growths are pedunculated. Multiple polypi in the stomach give characteristic roentgenologic findings but are rarely seen.

Of course, if a benign gastric lesion can be visualized gastroscopically, this is an extremely valuable aid in establishing a diagnosis.

Surgical exploration plus pathologic examination of the specimen is certainly the absolute method of final diagnosis. Because of the frequency of malignant changes in benign gastric lesion surgical exploration and removal of the tumor should not be delayed.

Because chronic diarrhea is such a prominent symptom in gastric polypi it seemed worth while to include at this time a short outline of etiological factors which produce diarrhea in adults so we might more easily see how diarrhea of gastric origin fits into the scheme of other chronic diarrheas.

* Received for publication March 12, 1941

Outline of etiologic factors which produce diarrhea

- 1 Ingesta, including food and drug poisonings
- 2 General toxic conditions, as sepsis, toxic goiter, Addison's disease, and Bright's disease
- 3 Deficiency diseases, as pellagra and spinae
- 4 Secondary circulatory disturbances producing chronic passive congestion of the gastrointestinal tract
- 5 Psychic disturbances
- 6 Organic disease of the gastrointestinal tract

A Organic disease above the colon

- 1 Gastrogenic
- 2 Pancreatogenic
- 3 Enterogenic

B Organic disease of the colon

Gastrogenic diarrhea was first described by Oppler in 1896 Eusterman and Balfour state that a gastrogenic diarrhea is the commonest type of chronic diarrhea in adults They also state that chronic diarrhea is one of the commonest disturbances seen in achlorhydria We realize that this information differs from other accepted theories on the subject and offer it chiefly because the case we are presenting showed these findings Alvarez has shown that any condition which favors rapid emptying of the stomach may produce a diarrhea This occurs because the rapid increase in bulk in the upper small bowel stimulates peristaltic activity which in turn may reflexly cause an increased number of bowel movements Probably most cases of gastrogenic diarrhea are a result of rapid emptying of the stomach We know that foreign bodies in the stomach are often associated with a diarrhea This is probably the result of increased irritability of the stomach by stimulation from the foreign body, with resulting increase in peristaltic activity and more rapid emptying of the stomach A polyp extending into the gastric lumen might well act the same as a foreign body and thus explain the diarrhea so commonly associated with gastric polyp

CASE REPORT

Mrs H A, a 35-year-old Greek dressmaker, was first seen August 10, 1940 Since May of 1939 the patient had had a persistent diarrhea with three to six stools during the day and two to four stools during the night Stools were always watery and occasionally contained mucus Once she passed bright red blood with her stool Her appetite remained excellent She had a few attacks of nausea and emesis Except for occasional crampy abdominal pain no other symptoms had been present Following eating, diarrhea was apt to increase The eating of meat in particular increased her diarrhea The patient had lost 30 pounds since the onset of the illness Nothing in her past history had any bearing on her present complaint

On physical examination the patient showed evidence of moderate weight loss Otherwise, nothing of importance was noted

Laboratory findings Urine was negative Red blood cell count was 3,410,000, hemoglobin 68 per cent, white blood cell count was 9,150, the differential count was normal Urea nitrogen, glucose, sodium chloride and carbon dioxide combining power were normal Wassermann reaction was negative Stools were positive for occult blood on three occasions, but negative for parasites and ova

Roentgenologic findings Stomach with barium showed a smooth polypoid structure extending from the greater curvature at about its midpoint into the lumen of the



FIG 1 Roentgenogram showing polypoid filling defect outlined with barium



FIG 2 Surgical field at time of operation showing polyp attached to gastric mucosa. Polyp and attached wall have been brought out through incision in the anterior gastric wall

stomach. The polyp was almost egg-sized and was freely movable in the lumen of the stomach except at its point of attachment along the greater curvature. Otherwise, the stomach was not unusual in appearance. The duodenal cap filled out well. At

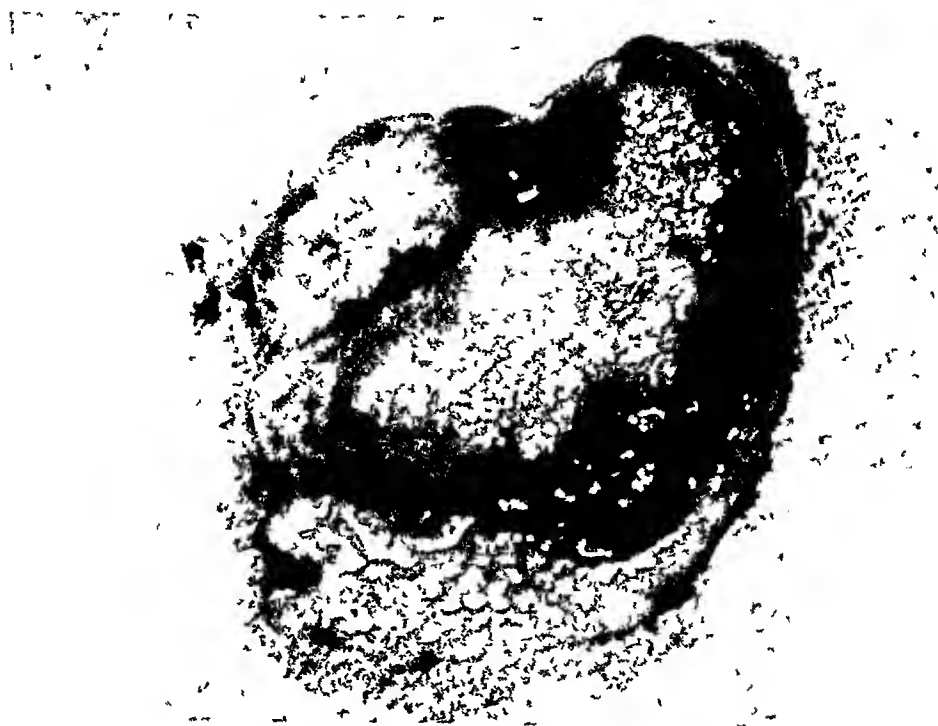


FIG 3 The excised polyp



FIG 4 Photomicrograph of section from the excised polyp

the end of five hours there was a slight trace of barium in the stomach partially outlining the polyp. Except for the gastric findings the gastrointestinal tract was normal. The colon did not show any pathology. Roentgenologic interpretation: solitary benign polyp of the stomach arising from the greater curvature.

Sigmoidoscopic examination was negative.

Gastroscopic examination: Just above the angulus on the greater curvature aspect there was a tumor mass bulging into the lumen of the stomach. It was redder in color than the surrounding mucosa. The surface was somewhat irregular. The upper portion of the tumor could not be seen. The mucosa of the remainder of the stomach showed marked atrophic gastritis.



FIG 5 Roentgenogram of stomach postoperatively showing smooth notching of greater curvature at site of surgical removal of the polyp.

Gastroscopic impression was "polypoid tumor mass on the greater curvature of the stomach. The nature of this tumor cannot be positively ascertained but would favor Grade I carcinoma."

Surgical findings On September 29, 1940, the polyp was excised from the posterior stomach wall and the wall of stomach repaired.

Pathological findings (Gross) Papilloma about 15 grams in weight measuring 5 by 4 by 2 cm. Microscopically it was a papillary adenoma of the stomach with marked chronic inflammatory changes throughout the stalk with considerable ulcerations on the surface. There was no evidence of malignancy.

Course Postoperatively the patient's course was uneventful except for a mild cystitis which rapidly disappeared. Her diarrhea subsided and bowel habits were about normal at the time of discharge on October 26, 1940. On October 25, 1940 the stomach was reexamined roentgenologically. Except for a smooth notching of the greater curvature at the point of resection of the tumor nothing unusual was demonstrated. The stomach was freely movable. On October 26, 1940 gastric analysis showed an absence of free hydrochloric acid.

DISCUSSION

This case presented a problem which in the first place would obviously be classified as a gastrointestinal disorder and secondly one in which we would expect to find the pathologic lesion located in the lower gastrointestinal tract rather than in the stomach. Cases presenting chronic diarrhea may very well have pathologic changes of the nature found here as the only initiating factor in the symptomatology and a careful analysis and study of the entire gastrointestinal system is of extreme importance.

We believe that the presence of the polyp in this woman's stomach and the marked atrophic gastritis and achlorhydria associated with it were the initiating factors in the marked diarrhea which she experienced. The patient stated that she was unable to eat any meat because of the marked diarrhea which it precipitated, and we assume that protein substances not acted upon by the gastric juices acted as an irritating factor and tended to increase peristalsis which in turn caused rapid emptying of the stomach. The polyp acting as a foreign body likewise tended to increase the activity of the stomach.

In a case report by Weitzen⁵ in the New York State Journal in January 1940, on the presence of a bezoar, the symptomatology was somewhat analogous to that noted in this case. In his case there was found in the stomach a ball of ingested thread, present for a long period of time and accompanied by diarrhea and chronic gastritis. There was a tremendous appetite with weight loss. All symptoms disappeared after removal of the bezoar.

In the case we have presented, following surgical removal of the lesion there was a complete cessation of symptoms. The patient received no medication.

The only treatment for benign gastric lesions is early surgical removal. The reasons for this are obvious.

It is necessary in order to relieve the patient's symptoms, and these lesions tend to undergo malignant changes.

We cannot emphasize too strongly the importance of complete gastrointestinal studies in cases of chronic diarrhea of obscure etiology. A negative barium enema does not mean that there is not some organic lesion in the gastrointestinal tract which is responsible for a chronic diarrhea.

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POST-RADIATION PANMYELOPHTHISIS CLINICALLY SIMULATING AGRANULOCYTOSIS*

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AMONG writers on hematology and roentgen therapy it has become customary to list, often with considerable qualification, excessive radiation as a potential cause of agranulocytosis^{1, 2, 3}. It was called to the attention of a member of this hospital staff who had cited such statements in a recent publication⁴ that examples of this type of reaction had been rarely if ever reported. Consequently, it was with extreme interest that we observed the course of the following case.

CASE REPORT

A 43 year-old-white woman was admitted to the Wisconsin General Hospital on September 7, 1939. Her chief complaint was of a mass in the abdomen. This was first noted during June of 1939. Other significant symptoms were anorexia, constipation, dyspnea on slight exertion, and progressive weight loss (60 pounds since December 1938). Her occupation was that of a housewife, and she admitted no exposure to benzene, coal tar derivatives, or drugs of any type. She had had occasional headaches which she called migraine. Physical examination revealed pallor, enlarged, very firm lymph nodes in the cervical, axillary and inguinal regions, pleural effusion on the left, enlarged liver and spleen and multiple firm, fixed intra-abdominal masses. There was a slight intermittent fever, with a maximum of 99.8° F. Hemoglobin was 12.2 grams. There were 4,740,000 red blood cells, 9,400 white blood cells, with 91 per cent neutrophils, 7 per cent lymphocytes, and 2 per cent monocytes. The Wassermann reaction was negative. Blood sugar, non-protein nitrogen, gastric acidity, urinalysis and the appearance of the upper gastrointestinal tract and colon on roentgen-ray study were within normal limits. A roentgenogram of the chest confirmed the findings of pleural effusion and demonstrated enlargement of the mediastinal lymph nodes and partial atelectasis of the left lower lobe. An electrocardiogram suggested toxic myocardial involvement. In a biopsied inguinal lymph node small round cells with scanty cytoplasm and large vesicular nuclei completely overgrew the gland, destroying the architecture and invading the capsule (figure 1).

A diagnosis of lymphosarcoma was made and roentgen therapy instituted. Exposing one fourth of the body surface at a time, a dose of 50-r† was twice given to each area in turn, and then 200-r was given to each of three abdominal pre-aortic node areas and to the splenic area. All radiation was given between September 15, 1939 and September 29, 1939, no more than one area being treated each day. Daily counts showed some fluctuation, but on September 27 the white blood cell level was still 6,900, on September 29, however, it fell abruptly to 950, and continued to fall thereafter.

Intensive therapy with large doses of pentnucleotide, intramuscular liver extract, and yellow bone marrow concentrate was promptly started, and three 500 c.c. transfusions given, but without apparent benefit. On October 3 there were 325 leukocytes,

* Received for publication January 20, 1941.

From the Department of Medicine, Wisconsin General Hospital and the University of Wisconsin Medical School.

† Factors

0.5 mm copper and 1.0 mm aluminum filters were used throughout.

For general body irradiation, FSD was 60 cm, at 160 kv and 7.5 milliamperes.

For abdominal nodes, FSD was 50 cm, at 175 kv and 15 milliamperes.

with 2.5 per cent neutrophils, 22.5 per cent eosinophils, 50 per cent small and 2 per cent large lymphocytes, 12 per cent young lymphocytic forms, 0.5 per cent monocytes, and 10.5 per cent cells which appeared to be of the lymphoid group but were so pathologically altered or primitive in form as not to be definitely classifiable. Platelets were estimated from the smear as a high normal in number, and the red count (4,735,000) and hemoglobin (14.7 gm) were well within normal limits. The total leukocyte count steadily decreased, reaching a final low on October 7 of 75, of which 94 per cent were lymphocytes, 4 per cent blasts, and 2 per cent primitive or unclassified

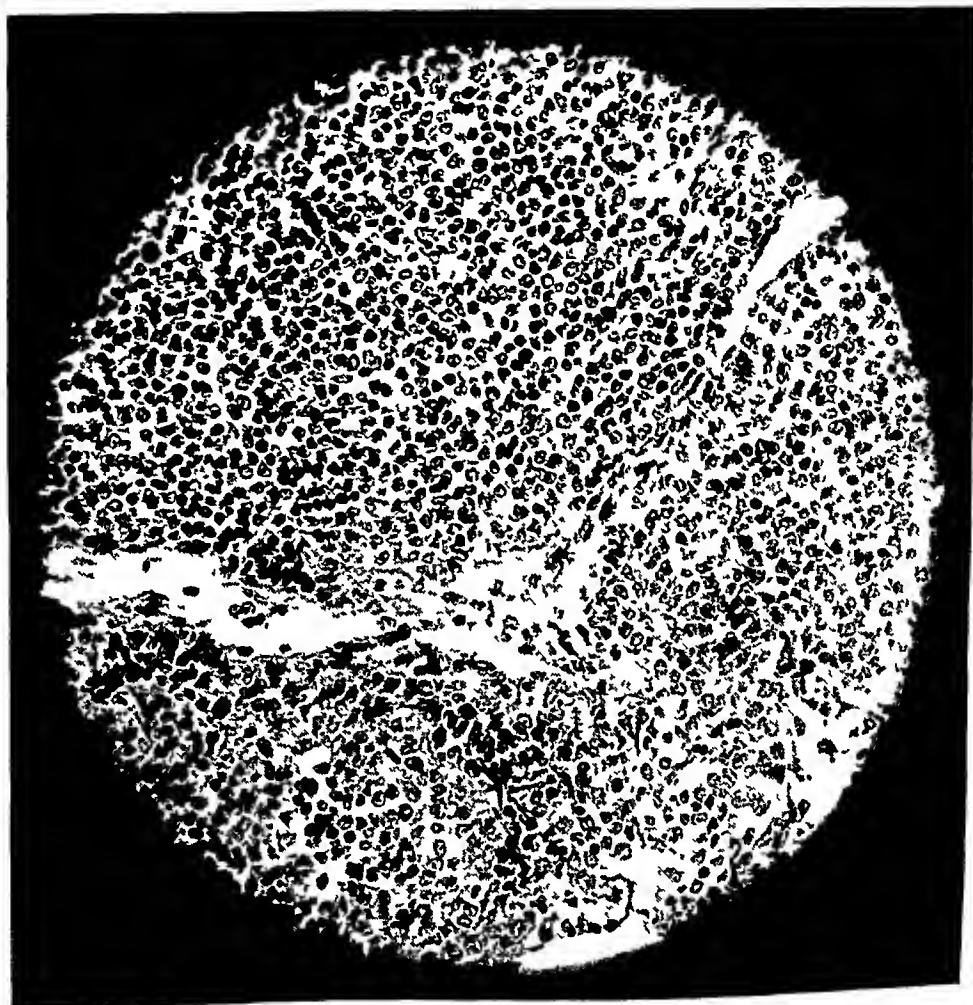


FIG 1 Photomicrograph of lymph node obtained by biopsy, showing lymphosarcomatous change ($\times 440$)

cells. Unfortunately, no hemoglobin nor red cell determinations were performed after October 4, but on this date, with the white count 450, hemoglobin was 12.2 grams, the same value as that on admission. On October 7 the red cells still appeared normal in the smears, but there was an apparent decrease in the number of platelets. On October 8, 23 days after beginning radiation therapy, the patient died.

A sternal biopsy on October 5 showed 0.2 per cent neutrophils, 4 per cent eosinophils, 63.4 per cent small, 5 per cent intermediate, and 6 per cent young lymphocytes, 0.6 per cent large young cells, 6 per cent unclassified cells, 1.4 per cent primitive cells, 3 per cent pathological cells, and 10.4 per cent plasma cells. Thirty normoblasts, one primitive red cell, and numerous polychromatophilic erythrocytes were seen during a count of 500 white cells.

The patient was remarkably free of symptoms and almost euphoric at times during this period. Anorexia, nausea and some pain at the site of pentnucleotide injections were the only complaints until the day preceding death, when a sense of substernal constriction, slight dyspnea, and a cough productive of a little sputum appeared. Between October 3 and October 8 she had a remittent fever varying between 99.8 and 102.8° F. There were never any oropharyngeal lesions, but at the sites of all intramuscular injections painful, indurated, dusky red to black areas appeared, and very few petechiae were seen. A faint scleral icterus was present the morning of October

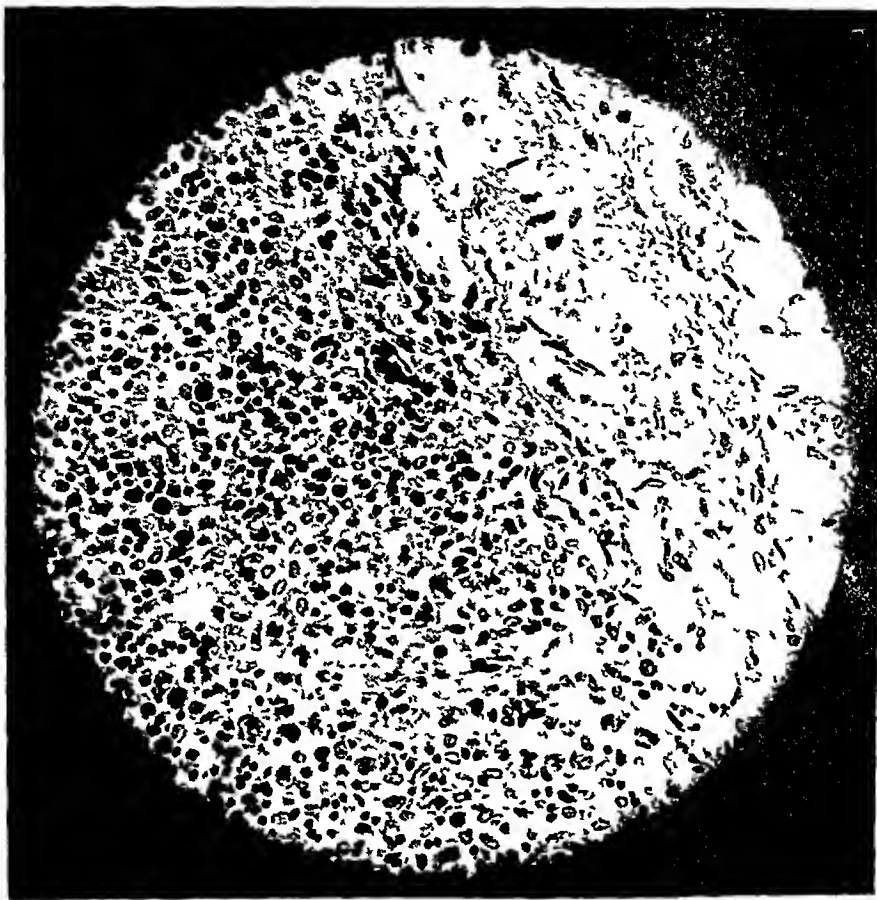


FIG 2 Photomicrograph of lymph node removed at autopsy, showing decrease in lymphoid elements, with pyknosis and fragmentation of nuclei and phagocytosis of degenerating cells. Some early fibrotic change is also visible. ($\times 440$)

8, and within a few hours a rapidly deepening generalized jaundice was seen. An icterus index performed on blood obtained a few minutes post mortem was 45.

Nembutal (totaling 4½ grains and last given approximately four weeks before exitus), acetyl salicylic acid (gr v on September 8), nicotinic acid (last dose September 26), ephedrine sulphate (gr ⅞ q i d from September 27 to October 5), and one dose each of morphine sulphate (gr ⅞) and scopolamine (gr ⅛₁₀₀) were the medications received during her hospitalization, in addition to the drugs given in an effort to combat the progressive granulocytopenia. None of these drugs is to our knowledge considered a cause of agranulocytosis.

Necropsy. Gross examination¹ showed an obese, generally icteric female with purplish black swollen areas of necrosis on the arms, thighs, and buttocks. The left lung was almost completely atelectatic, with 1700 cc of icteric fluid occupying the remainder of the left pleural cavity. The right lung was crepitant throughout, and free of gross lesions except at the base where a 5 cm area of hemorrhage was present. The mediastinal nodes formed a large, firm, irregular mass, dry and mottled pinkish gray on section. The heart was small (270 gm), flabby, and showed early brown atrophy. There was slight coronary and aortic atherosclerosis. The spleen weighed

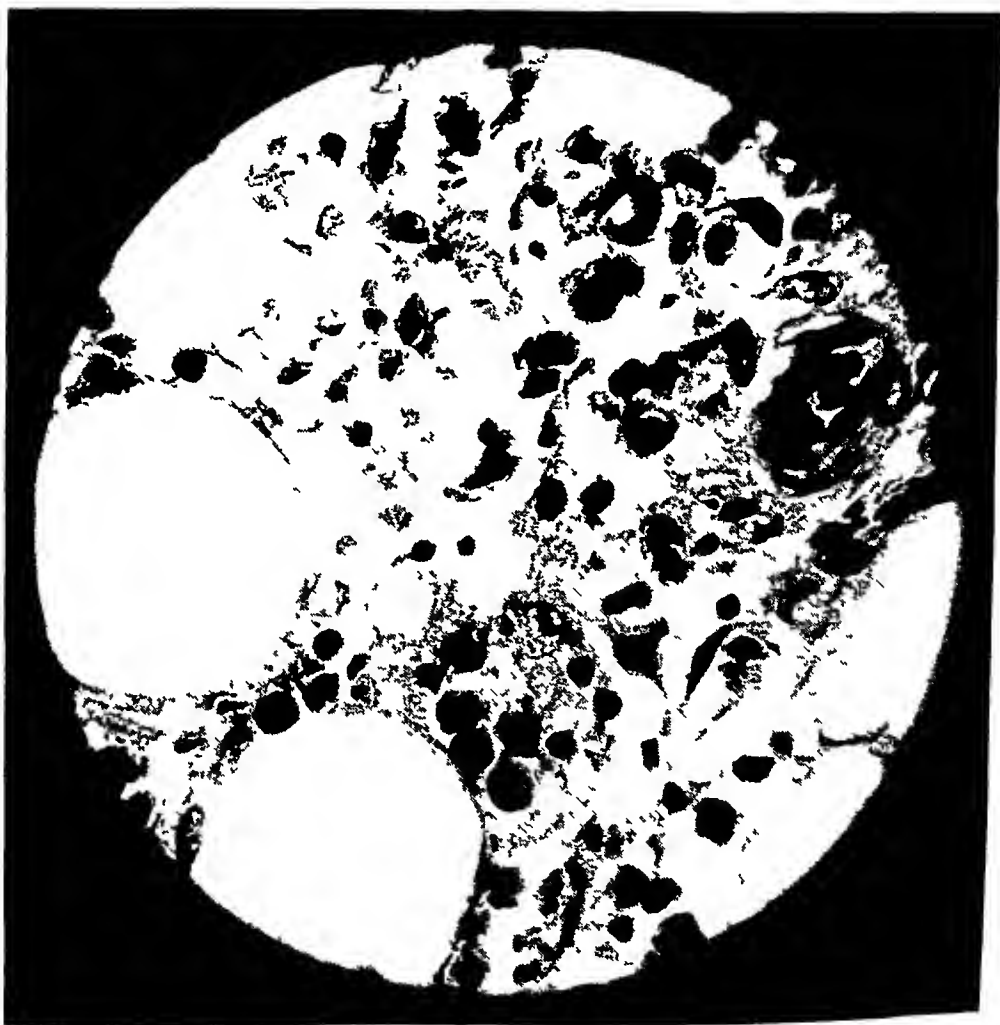


FIG 3 Vertebral marrow ($\times 950$) obtained at autopsy. Loss of cellularity with relative increase in numbers of lymphocytes and plasma cells, general degeneration of hematopoietic elements, and some fibrinous exudate may be seen.

650 gm, was dark purple in color, and quite firm in consistency. There were firm matted masses of lymph nodes in the retroperitoneal and pelvic areas, in the mesentery, and about the stomach and pancreas. The bone marrow was dark red.

Microscopic examination. The lymph nodes showed loss of normal architecture and atrophy of lymphoid elements, with much fibrosis, many phagocytes filled with lipid material, and many endothelial cells, as well as small areas of hemorrhage (figure 2). The discolored areas of the right lung showed extensive hemorrhage containing many bacterial colonies; similar clumps of bacteria were present in the areas of sub-

* Performed by Dr Leonard Long

cutaneous necrosis There was chronic passive congestion of the lungs, liver, and spleen The spleen also showed loss of architecture, atrophy of the lymphoid and increase in the endothelial elements, considerable fibrosis and endarteritis, areas of hemorrhage and hyaline necrosis in the pulp, and a number of eosinophiles Bone marrow from the ribs, sternum, vertebrae, and femur all showed a great many disintegrating cells, many pyknotic and fragmented nuclei, some hyaline necrosis, disintegrating scanty megakaryocytes, a network of fibrinous material in many areas, areas of hemorrhage, and some beginning fibrosis, especially about the blood vessels A considerable number of large reticuloendothelial cells were seen, as were a few lymphocytes and an occasional plasma cell Erythropoietic and myelopoietic centers were few and relatively inactive, many showing distinct necrosis (figure 3) The few fairly normal appearing areas were mainly in the femoral marrow, where there also appeared to be a slight increase in the number of eosinophiles Postmortem blood culture showed *Staphylococcus aureus* Other findings were not remarkable

It is probable that the relatively longer life span and greater resistant qualities of the red cells masked the destructive changes in their formative elements until the time of death, and that these changes would have become apparent had the patient lived longer Similar factors may have conditioned the relative eosinophilia in the earlier counts Clinically there was nothing to suggest that this was not a true agranulocytosis, although the laboratory finding of a suggestively low percentage of normoblasts in the sternal biopsy specimen might have been considered of possible significance Consequently, the post-mortem finding of marrow damage so extensive and severe as to amount almost to a complete aplasia of all the hematopoietic elements was unexpected, and suggested that an examination of the literature in regard to this point might prove of interest

In spite of a careful, thorough search, no clear cut, fully reported cases of pure agranulocytosis secondary to radiation could be found, although cases reported by Lovett,⁵ Fiessinger and associates,⁶ and in the review of Bock and Wiede⁷ are quoted as such, e g, by Rosenthal³ Lovett, in a report on a case of agranulocytosis, says in passing, of another case "In a patient operated on for carcinoma of the prostate and treated afterward with roentgen-rays and radium, the white count fell to 200 cells per cubic millimeter, with only 4 per cent of polymorphonuclear leukocytes He developed angina of a type similar to that of our patient before death" No further details are given, however, so it is not possible to be sure just what process may have occurred Fiessinger's case was a woman of 63 who, when first seen with a condition diagnosed as cholecystitis, had a leukocyte count of 13,200, of which 67.5 per cent were lymphocytes and 28 per cent neutrophils Nine months later, following a 'grip-pal coryza,' a large spleen was discovered Roentgen-ray therapy to the spleen was commenced, although the authors state that they made no pretense of diagnosing the cause of the splenomegaly Four treatments of "34 filtres par 5/10 de nullimetre d'aluminium"* were given at weekly intervals There was no application over the long bones Six days after the fourth treatment slight fever and extreme fatigue were noted Blood count showed red blood cells 41, white blood cells 330, neutrophils 0.3 per cent, eosinophiles 2 per cent, basophiles 1 per cent, large monocytes 14 per cent, medium-sized monocytes 75 per cent, lymphocytes 15 per cent, and neutrophilic myelocytes 2 per cent (total 109.3 per

* No unit of dosage was given by the author

cent?) Intramuscular injections of milk were given, with a prompt rise to 10,000 white blood cells with 79 per cent neutrophils. The authors state that "this is without doubt a syndrome of agranulocytosis", indeed, it may well have been. But the preexisting splenomegaly and relative neutropenia, without satisfactory explanation, leave something to be desired regarding the diagnosis and possible etiology. The review of Bock and Wiede refers to two cases of their own, one an assistant physician and one a nurse in a radium station, who were found to have, respectively, white counts of 5,100 with 34 per cent granulocytes and 6000 with 46 per cent granulocytes, and in a review of the literature regarding agranulocytosis, to the cases of Siegels⁸ as cited by Flaskamp.⁹ Little further information regarding their own cases is given, though they were said to be slowly improving at the time of publication, but on the basis of their description it would be difficult to classify them as true agranulocytosis. Siegels' report is a study of the peripheral blood in 15 patients carefully followed for 10 days to two years after radiation for various pelvic disorders, and in nine workers in his clinic. In only one of his 280 post-radiation counts did the total white count fall below 3300, or the neutrophil count below 2000, and in this case a count of 2200 white blood cells with 1936 neutrophils was found 10 days after treatment for an inoperable carcinoma. Simultaneous hemoglobin value was 43 per cent and red count 3,020,000. He records two other absolute neutrophil counts between 2000 and 2800, and eight between 2800 and 3000. It seems rather doubtful that these cases can be considered as agranulocytosis.

Not only were no definite cases of agranulocytosis found, but reported experimental observations on the hematological effects of radiant energy lend little support to the idea that there is any selective action on the granulocytic system. Instead, such effects seem to be differentiated purely on a quantitative and chronological basis, and to be modified in their reflection in the peripheral blood picture by the relative length of life of the adult form of each cell type. Further, the changes seem to be purely destructive. Nothing was encountered to suggest that a stem cell or myeloblastic hyperplasia without maturation, such as is described in many cases of agranulocytosis, is ever seen as a result of radiation. The resemblance to the group of agranulocytoses described as having hypoplastic marrow, among which Schultz' original case¹⁰ apparently belongs, is somewhat greater, at least as regards the granulocytic series. In such cases, however, Darling, Parker, and Jackson¹¹ found only marked depletion in numbers of the granulocytic stem cells, with a total absence of more mature forms. There was replacement by lymphocytes and myriads of plasma cells, but nothing in the nature of the acutely degenerative changes which are seen after exposure to roentgen-rays. Custer¹² did find degeneration and necrosis in his most acute cases, but even here they were limited almost entirely to the granulocytic cells.

From the many excellent studies on blood diseases due to exposure to roentgen-rays, e.g., Brinnitzer¹³ and Flaskamp,⁹ and on the blood and marrow findings after therapeutic radiation, e.g., Minot and Spurling,¹⁴ Selling and Osgood,¹⁵ and Casati, a composite idea of the resultant changes may be postulated. This would suggest that a given amount of radiation will affect all cell types, but in different degrees, lymphoid tissue being most susceptible, erythropoietic least, the granulocyte and megakaryocyte series intermediate, and that the latent periods vary. There seems to be first a rise and then a fall in the

absolute lymphocyte count, overlapped by a similar change starting a little later and proceeding more slowly in the neutrophile group. If the damage be severe enough the erythrocyte count may later fall, but often the longer life span of the circulating red cells and the lower sensitivity of the erythropoietic elements are adequate to prevent any peripheral manifestation of the changes in the red series. Monocytes, eosinophiles, and basophiles seem to resemble the neutrophiles in their reaction, but with a slightly lower degree of susceptibility, reports in regard to them are few and conflicting. Findings with respect to platelets vary also, but the majority opinion seems to be that they follow an intermediate course between that of the red and white cells.

Of interest in this respect is another case recently admitted on the pediatric service in this hospital. A boy 10 years old had been diagnosed as having acute leukemia, and over a period of four weeks before admission had received radiation totaling 2635-r over the splenic, cervical, mediastinal and axillary areas. Additional radiation of 700-r (100-r at each of seven treatments in a period of eight days) over the splenic area was given here. The patient died one month after the last roentgen-ray treatment. Sternal, vertebral and rib marrow obtained at necropsy showed an extensive and active fibrotic process with almost complete absence of hematopoietic elements.

SUMMARY

1 A case of post-radiation panmyelophthisis which clinically simulated agranulocytosis has been presented.

2 A search of the literature failed to reveal any clear cut, fully reported cases of agranulocytosis due to radiation.

3 A review of the published reports of the effects of radiation on hematopoietic tissues suggests that the occasional appearance of what seems to be severe uncomplicated neutropenia due to roentgen-rays is actually a manifestation of a generalized marrow damage. The peripheral reflection of this damage has been modified by the interplay of the varying life spans and by the rates of reaction of the various cell types, rather than by any isolated effect on the neutrophilic series, either of a destructive or of a maturation inhibiting type.

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EDITORIAL

SULFADIAZINE

Less than eight years ago Domagk published his initial report on the striking effects of the brick-red dye prontosil in experimental hemolytic streptococcal infections in mice. Shortly thereafter it was found that a relatively simple chemical compound, sulfanilamide, or para-amino-benzene-sulfonamide, was the active constituent of prontosil. These discoveries marked the dawn of a new era in the chemotherapy of bacterial infections. As a result a stupendous amount of experimental work has been carried out and the medical literature has been flooded with articles on the effects of the various sulfonamides in the treatment of infectious diseases. Many new compounds have been synthesized, tested out in the laboratory, and then administered to patients. We have seen in succession sulfanilamide, neo-prontosil, sulfapyridine, sulfathiazole, and finally sulfadiazine added to our therapeutic armamentarium. With such a variety of drugs to choose from the chief problem that confronts the physician today is the selection of the most effective drug for the treatment of a given infection.

Sulfanilamide was found to be highly active against infections due to the beta hemolytic streptococcus, meningococcus, gonococcus and Welch bacillus, but relatively ineffective against pneumococcal infections. Unfortunately this drug gave rise to a number of toxic manifestations in many patients. One of the more serious toxic effects was acute hemolytic anemia which developed during the first week of therapy in about 3 per cent of all patients receiving sulfanilamide. Fatal granulocytopenia was encountered occasionally in patients who had taken the drug for over two weeks. Hepatitis (occasionally acute yellow atrophy), peripheral neuritis, and psychosis were other infrequent but serious toxic effects. In addition to these serious toxic effects which are relatively rare, minor complaints such as headache, dizziness, nausea, anorexia, or mental confusion were common to the majority of patients treated with sulfanilamide. Drug fever and dermatitis were by no means rare. Cyanosis, due either to methemoglobinemia or to a colored by-product of sulfanilamide, was more alarming to the family than to the physician since it was rarely of serious import. Acidosis with a fall in the carbon dioxide combining power of the blood was frequently a disturbing feature until it was found that this complication could be prevented by administering sodium bicarbonate with each dose of sulfanilamide. Because of these multiple toxic and unpleasant side-effects, sulfanilamide has largely given way today to the less toxic sulfadiazine as the drug of choice for the treatment of hemolytic streptococcal, meningococcal, and Welch bacillary infections. Sulfanilamide still maintains a definite though limited position among the sulfonamide drugs. In therapeutic doses sulfanilamide has not caused renal damage (gross hematuria or anuria) such as occurs in a small

but significant proportion of patients treated with sulfapyridine, sulfathiazole, or sulfadiazine. Therefore sulfanilamide is still the drug of choice for the treatment of patients with hemolytic streptococcal infections complicated by hemorrhagic nephritis or other serious renal disorders. Furthermore, powdered sulfanilamide, because of its greater solubility and diffusibility, has been found superior to its three more modern derivatives for local implantation in the treatment of traumatic wounds or infections in the peritoneal cavity.

Sulfapyridine was first employed extensively in the treatment of pneumococcal pneumonia in the winter of 1938-1939. The results were dramatic and the case fatality rate in lobar pneumonia was reduced by nearly two-thirds. Here at last was a drug that proved to be highly effective against the pneumococcus. Unfortunately, however, several difficulties arose in connection with the administration of sulfapyridine. Because of its low solubility, absorption from the gastrointestinal tract was often slow and many hours were required to obtain an effective blood level of the drug. This obstacle was surmounted by the administration of an initial intravenous injection of 4.0 grams of the relatively soluble sodium salt of sulfapyridine, followed by the oral administration of 1.0 gram of sulfapyridine every four hours as a maintenance dose. The worst feature of sulfapyridine therapy was the extremely high incidence of nausea and vomiting (of central origin) following the administration of the drug either orally or intravenously. At times dehydration from severe vomiting necessitated the intravenous administration of saline and glucose. Patients were frequently heard to say that they would prefer to take their chances with the disease rather than the cure. It became obvious that, although sulfapyridine was an extremely potent anti-pneumococcal agent, it was a long way from an ideal solution of the pneumonia problem.

In 1939 sulfathiazole succeeded sulfapyridine as the drug of choice for the treatment of pneumococcal infections. This compound was more soluble than sulfapyridine and hence more readily absorbed. The incidence of nausea and vomiting from sulfathiazole was much lower than that from sulfapyridine. Sulfathiazole is more rapidly excreted than sulfapyridine and it is, therefore, difficult to maintain an effective blood level of the drug. Furthermore, sulfathiazole has subsequently proved to be the most toxic of the four sulfonamide compounds in general use today, giving rise to a higher incidence of serious toxic effects such as drug fever, dermatitis, hepatitis, granulocytopenia, hemolytic anemia, and renal complications. Rich¹ has very recently demonstrated periarteritis nodosa-like lesions in the tissues of patients who have been treated with sulfathiazole. Evidences of renal damage in the form of gross hematuria as a result of the precipitation of drug

¹ RICH, A. R. The rôle of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy, *Bull. Johns Hopkins Hosp.*, 1942, lxxi, 123-140.

crystals in the kidneys or oliguria due to direct toxic damage to the renal tubules have been noted in a large enough proportion of patients treated with sulfapyridine or sulfathiazole to necessitate careful observation of the urine and fluid balance in all patients receiving these drugs

Finally in 1940 sulfadiazine was introduced in the hope that it would surpass sulfathiazole as an antipneumococcal agent. Two years later we find that sulfadiazine has stood the test of time as the drug of choice for the treatment of pneumococcal lobar pneumonia. Sulfadiazine is fairly well absorbed from the intestinal tract. It is less rapidly conjugated and more slowly excreted than sulfathiazole, and is just as effective. Most important of all, sulfadiazine is far less toxic than sulfapyridine or sulfathiazole. In a recent review of a large number of cases treated with one or another of the four drugs, Long² found the incidence of serious toxic effects such as drug fever, dermatitis, acute hemolytic anemia, granulocytopenia, renal complications, hepatitis, peripheral neuritis, and psychosis to be as follows: sulfathiazole 18.6 per cent, sulfapyridine 15.9 per cent, sulfanilamide 11.9 per cent, and sulfadiazine 6.5 per cent. Thus sulfadiazine is only about one third as toxic as sulfathiazole. Acute hemolytic anemia from sulfadiazine must be extremely rare.

Elsewhere in this issue Finland and his associates³ advocate sulfadiazine as the drug of choice for the treatment of hemolytic streptococcal, pneumococcal, meningococcal, and Friedlander bacillary infections. They recommend sulfadiazine in all acute pulmonary infections and acute meningitides, also in gonococcal or staphylococcal infections where prolonged therapy is desirable. This report is in general accord with the attitude of other authorities in the field, notably Long, Dowling, Flippin, Trevett, and Wood. The reasons for this viewpoint are twofold: (1) equal or superior efficacy of sulfadiazine in the treatment of the infections mentioned, and (2) low toxicity. Sulfadiazine is not the ultimate answer to the problem of chemotherapy for bacterial infections, but it is by far the best of the sulfonamide compounds available at the present time. Its shortcomings are apparent: (1) low solubility with relatively slow absorption, a difficulty which may be circumvented, as in the case of sulfapyridine or sulfathiazole, by an initial intravenous injection of the sodium salt of sulfadiazine, (2) toxicity, in particular drug fever, dermatitis, and renal damage, and (3) cost (the price of sulfadiazine is still considerably higher than that of any of the other three compounds). These disadvantages are more than outweighed by the special merits of the drug. Patients receiving sulfadiazine rarely complain of unpleasant symptoms such as headache, dizziness, malaise, nausea or vomiting. The valency of the drug is much wider than that of any one of its predecessors. True, sulfathiazole and sulfapyridine are still

² LONG, P. H. Personal communication to the author.

³ FINLAND, M., PETERSON, O. L., and GOODWIN, R. A. Sulfadiazine: further clinical studies of its efficacy and toxic effects in 460 patients, *ANN INT MED*, 1942, **xvii**, 920-934.

regarded as being superior to sulfadiazine for treatment of acute gonococcal infections and certain infections of the urinary tract. Yet sulfadiazine already gives promise of supplanting the other sulfonamides as the drug of choice in many of these genito-urinary infections. Further investigation is necessary before final conclusions can be drawn.

All in all, sulfadiazine stands out as the most effective and least toxic of the sulfonamides available to the physician today. At the moment it is the king of the sulfonamides.

W H B

REVIEWS

Text Book of Clinical Parasitology By DAVID L. BELDING, M.D. 888 pages; 25 × 16 cm 1942 D Appleton-Century Co., New York Price, \$8.50

This book contains an excellent comprehensive survey of the entire field of human parasitology, including the arthropod vectors of disease as well as the parasitic protozoa and helminths. It is more comprehensive than the title "Text Book" might suggest. Although attention is given primarily to the commoner parasites of greatest practical importance, a large number of rare or occasional parasites receive brief but adequate consideration.

The author has followed a uniform procedure in discussing each parasite: history, geographical distribution, biological characteristics, life cycle, pathogenesis, symptomatology, immunity, diagnosis, prognosis, treatment, and prevention. This is an advantage from the standpoint of clarity and ease in finding desired information, although it results in considerable repetition. He has stressed the clinical features more than the average text book, but the consideration of the zoological phases of the subject is the more authoritative.

The most distinctive feature of the book is the large number of tables (44) and diagrams which are very useful both from the standpoint of teaching and of finding essential information quickly. The book is profusely illustrated. There are many simple line drawings so arranged as to facilitate the identification or differentiation of related species. The geographical distribution of the important parasites and the life cycles are graphically demonstrated.

The book closes with a useful section on technical methods and on parasitocidal and anthelmintic drugs.

The work is well up to date, and is documented with numerous references. It is a valuable contribution and is recommended to those interested in the subject.

P. W. C.

Modern Drug Encyclopedia and Therapeutic Guide Second Edition By JACOB GUTMAN, M.D., Ph.D., F.A.C.P. 1644 pages, 24 × 16 cm 1941 New Modern Drugs, New York Price, \$10.00

The second edition of this very useful reference book is cordially welcomed by the many admirers who were familiar with the first edition published in 1934. The author remarks that since 1934 many remarkable advances as well as many vital changes have been made in drug therapy which are of paramount importance to the medical profession.

Accurate and concise information is presented concerning all the popular non-pharmacopoeial preparations including biologicals, allergens, potent drugs and endocrine products with the name of the manufacturer, brief description, action and uses, how supplied, dosage and administration.

The material is satisfactorily arranged, the reference is readily made, and those who are accustomed to having the volume on their desks or on a nearby shelf would miss it sadly if removed.

A quarterly supplement helps one keep up to date.

I. P. S.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Sulfamylamide and Related Compounds in General Practice.* Second Edition By WESLEY W SPINK, M.D , F A C P 374 pages, 21 × 14.5 cm 1942 Year Book Publishers, Inc , Chicago Price, \$3.00
- Diseases of the Liver, Gallbladder and Bile Ducts* By S S LICHTMAN, M D , F A C P 906 pages, 24 × 15.5 cm 1942 Lea and Febiger, Philadelphia Price, \$11.00
- Changes in the Knee Joint at Various Ages* By GRANVILLE A BENNETT, M C , HANS WAINE, M D , and WALTER BAUER, M C 97 pages of text plus 31 plates, 26 × 17.5 cm 1942 The Commonwealth Fund, New York Price, \$2.50
- Hemolytic Syndromes* By WILLIAM DAMESHEK, M D , TIBOR J GREENWALT, M D , RUSSELL J TAT, M D , and CAMILLE DREYFUS, M D 41 pages, 31 × 24 cm 1942 Privately printed (A reprint of an exhibit sponsored by the New England Medical Center, Boston Presented at the 1942 Convention of the American Medical Association, Atlantic City, June 1942) Price, \$1.50
- Thoughts of a Psychiatrist on the War and After* By WILLIAM ALANSON WHITE, M D 28 pages, 26 × 18 cm 1942 The William Alanson White Psychiatric Foundation, Inc , Washington, D C (Republished essay—originally copyrighted by Paul E Hoeber in 1919) Price, \$1.50
- Osler's Principles and Practice of Medicine* Fourteenth Edition By HENRY A CHRISTIAN, M D , F A C P 1500 pages, 25 × 17 cm 1942 D Appleton-Century Co , New York Price, \$9.50
- Blood Substitutes and Blood Transfusion* Edited by STUART MUDD, M A , M D , and WILLIAM THALHIMER, M D Seventy Collaborating Investigators 407 pages, 24.5 × 16 cm 1942 Charles C Thomas, Springfield, Illinois Price, \$5.00

COLLEGE NEWS NOTES

ADDITIONAL A C P MEMBERS IN THE ARMED FORCES

Previously reported in these columns were the names of 973 members of the American College of Physicians serving in the armed forces of their country. Herewith are reported the names of 92 additional members, bringing the grand total to 1,065.

Elsewhere in these columns appears an age analysis of members of our College. Considering the fact that the average age of all members of the College, Masters, Fellows and Associates, is 48.9 years, the number, 1,065, on active duty from a total membership of approximately 4,800, is indeed impressive.

David I. Abramson
Wardner D. Ayer

Orpheus J. Bizzozero
Oscar Blitz
Allen G. Brailey
Russell S. Bray
Osborne A. Brines
Norton S. Brown
Philip W. Brown
L. Clair Burket

Horace B. Cates
Olin B. Chamberlain
Richard E. Ching
Morgan Cutts
Casimir J. Czarnecki

John S. Davis, Jr.
William F. Dobyns
Charles H. Drenckhahn
Early D. DuBois
Garfield G. Duncan

Edwin G. Faber
Henry Felson
Arthur N. Ferguson
John W. Ferree
Maurice P. Foley
John V. Fopeano
Meyer Friedenson
Louis Friedfeld

John F. Giering
Wilton R. Glenney
Douglas M. Gordon
George A. Gray
Harold J. Gunderson
Ramsdell Gurney

Everett E. Hammonds
Ben R. Heninger
Meredith B. Hesdorffer
Edward D. Hoedemaker
Arthur A. Holbrook
A. Gerson Hollander
Roy H. Holmes
Benjamin Horn
Lyman H. Hoyt

Alfred P. Ingegno

Robert R. Janjigian
William N. Jenkins
Thomas A. Johnson

Samuel R. Kaufman
Henry B. Kirkland
Elmer A. Klee field

Charles A. Landshof
Aleksei A. Leonidoff
John B. Levan

Willard Machle
A. Seldon Mann
John K. Martin
William S. McCann
Charles A. McKendree
J. Stuart McQuiston
Jonathan C. Meakins
Oliver J. Menard
George W. Millett
John H. Mills
John B. Morev
Frank R. Mount

Algot R. Nelson
Arthur D. Nichol

George C Owen

Ivan Thompson

Felix R Park

David Ulmar

Julius R Pearson

L Lewis Pennock

A Robert Peskin

William von Stein

Herbert W Rathe

Harold F Robertson

William W Rucks, Jr

Joseph Weinstein

Joseph F Whinery

Thomas J White

Henry M Winans

Andrew C Woofter

Arthur T Wyatt

Leo V Schneider

Maurice A Schnitker

Fred F Senerchia, Jr

Edward V Sexton

Kenneth K Sherwood

J Shirley Sweeney

Lloyd B Young

John I Zarit

AVERAGE OF A C P MEMBERS 48 9 YEARS

A recent analysis of the ages of the members of the American College of Physicians, as of October 15, 1942, reveals that the average age of the 4 Masters is 74 3 years, the average age of the 3,705 Fellows is 51 3 years, and the average age of the 1,110 Associates is 40 9 years. The average age for the entire membership of Masters, Fellows, and Associates is 48 9 years.

The following table gives the distribution in various age groups. In the highest age group there is 1 Fellow 94 years of age, 1 Fellow and 1 Associate 89 years of age, 1 Fellow 88 years of age, 1 Fellow 85 years of age, and 1 Master, 15 Fellows, and 2 Associates between 80 and 84.

Associates in the higher age groups constitute a group who became Associates in 1926 by virtue of being members of the American Congress on Internal Medicine, and who, by the terms of the merger of the Congress with the College, were not required to present credentials for advancement to Fellowship.

Age Group	90-94	85-90	80-84	75-79	70-74	65-69	60-64	55-59	50-54	45-49	40-44	35-39	30-34	26-29	Total
Associates		1	2	11	12	24	22	29	49	113	199	373	258	17	1,110
Fellows	1	3	15	47	119	261	380	462	680	662	624	384	67		3,705
Masters			1		2	1									4
	1	4	18	58	133	286	402	491	729	775	823	757	325	17	4,819

NEW LIFE MEMBER

Dr James Murray Flynn, F A C P, Rochester, N Y, became a Life Member of the American College of Physicians on October 10, 1942.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members

Books

- Dr Francis R Dieuaide, F A C P, Boston, Mass—"Civilian Health in Wartime",
 Dr Edward J Stieglitz, F A C P, Washington, D C—"Abnormal Arterial Tension",
 Dr Carl J Wiggers, F A C P, Cleveland, Ohio—"Selected Reprints from the Department of Physiology of Western Reserve University School of Medicine," two bound volumes

Reprints

- Dr George E Baker, F A C P, Casper, Wyo—1 reprint,
 J Edward Berk (Associate), Captain, (MC), U S Army—3 reprints,
 Dr J Bailey Carter, F A C P, Chicago, Ill—10 reprints,
 Dr William Herbert Ordway, F A C P, Mt McGregor, N Y—1 reprint,
 George C Owen (Associate), Major, (MC), U S Army—1 reprint,
 Dr Louis L Perkel, F A C P, Jersey City, N J—1 reprint,
 Dr William Kendrick Purks, F A C P, Vicksburg, Miss—2 reprints
 Herbert W Rathe, F A C P, Captain, (MC), U S Army—1 reprint,
 Dr Edward J Stieglitz, F A C P, Washington, D C—17 reprints,
 Dr Paul F Whitaker, F A C P, Kinston, N C—5 reprints,
 Dr Burton L Zohman, F A C P, Brooklyn, N Y—1 reprint

The Department of Pharmacology of the George Washington University School of Medicine, Washington, D C, contributed a bound volume entitled, "Studies from the School of Medicine, The George Washington University, 1941-1942," as a gift to the College Library

LUNCHEON MEETING HELD BY VIRGINIA MEMBERS, A C P

Dr J Edwin Wood, Jr, F A C P, Acting Governor of the College for Virginia, reports a luncheon meeting of the Virginia members in Roanoke in early October. Following the luncheon a business session was held. Dr R Finley Gayle, F A C P, Richmond, presided as Regional President. Dr Ernest G Scott, F A C P, Lynchburg, was made Regional President for the coming year. Dr Alexander F Robertson, Jr, F A C P, Staunton, was reelected Secretary-Treasurer. The meeting was highly successful with a very good attendance. It was determined not to hold a regular autumn State meeting of the College members as in previous years, due to transportation difficulties and the inability of many physicians to attend.

MICHIGAN STATE MEDICAL SOCIETY WILL HOLD 1943 ANNUAL MEETING

The Executive Committee of the Council of the Michigan State Medical Society has determined to continue its annual meetings and will hold its 78th such meeting at the Statler Hotel, Detroit, during the week of September 20, 1943. Monday and Tuesday of the week will be given to the meeting of the House of Delegates, of which Dr P L Ledwidge, F A C P, Detroit, is the Speaker. Wednesday, Thursday, and Friday will be given to a streamlined program of general assemblies.

At the recent meeting of the Society, Dr H H Cummings, Ann Arbor, was installed as President and Dr C R Keyport, Grayling, was named President-Elect.

Dr Frederick T Zimmerman (Associate) is now associated with Columbia University College of Physicians and Surgeons, New York, N Y, his specialty being

experimental neurology Dr Zimmerman is Research Assistant in the Department of Neurology and Instructor in Neurology and Psychiatry in the University Extension Division He is also Junior Assistant Neurologist at the New York Neurological Institute

On September 29, 1942, Dr Herbert T Kelly, F A C P, Philadelphia, Pa, spoke on "Dietary Deficiencies Exaggerated by Therapeutic Diets" at the meeting of the Lackawanna County Medical Society in Scranton and on October 3 he spoke on "Nutrition in Industry" at a meeting of the Pennsylvania Railroad Surgeons in Pittsburgh On October 22 Dr Kelly conducted a symposium on "Medical Aspects of Parodontosis" and an exhibit on dietary deficiency diseases at a meeting of the Fifth District Dental Society in Harrisburg

Among those who will speak at the Friday Afternoon Lecture Series for 1942-1943, sponsored by the New York Academy of Medicine, are
 January 29, 1943—Dr S Bernard Wortis, F A C P, New York, N Y—"Modern Treatment of the Psychoses",
 February 19, 1943—Dr Robert L Levy, F A C P, New York, N Y—"Clinical Types of Coronary Insufficiency and Their Recognition",
 February 26, 1943—Dr Maurice Bruger (Associate), New York, N Y—"Recent Advances in the Clinical Interpretation of Laboratory Data",
 March 19, 1943—Harold J Harris (Associate), Lieutenant Commander, (MC), U S Navy—"Brucellosis Diagnosis, Differential Diagnosis and Treatment"

Dr Robert K Dixon, F A C P, Denver, Colo, has been appointed a member of the Colorado State Board of Medical Examiners

Dr R Garfield Snyder, F A C P, New York, N Y, discussed "Recent Advances in the Treatment of Arthritis" at a recent meeting of the Bridgeport (Conn) Medical Society

Dr Paul A O'Leary, F A C P, Rochester, spoke on "Technic for Intravenous and Intramuscular Administration of Antisyphilitic Remedies" at the annual session of the Southern Minnesota Medical Association, September 28, 1942

Dr Alexander H Stewart, F A C P, Harrisburg, has been appointed Secretary of the Pennsylvania Board of Health Dr Stewart served as Deputy Secretary from 1939 to 1941 and since 1941 had been serving as Acting Secretary

The Association of American Medical Colleges held its fifty-third annual meeting in Louisville, Ky, October 26-28, 1942 Among those who spoke were
 Dr Hugh R Leavell, F A C P, Louisville, Ky—"Coordinating Program of Health, Hospital and Medical School in a Municipal University",
 Dr E Cowles Andrus, F A C P, Baltimore, Md—"Medical Research in Wartime",
 Dr S Spafford Ackerly, F A C P, Louisville, Ky—"The Teaching of Psychiatry to Undergraduate Medical Students",
 Dr Russell M Wilder, F A C P, Rochester, Minn—"Teaching of Nutrition"

During August Dr George E Burch, F A C P , Instructor in Medicine at Tulane University School of Medicine, New Orleans, conducted a graduate course in internal medicine and cardiovascular diseases at the Hospital Santo Tomás, Panama City, R P

John L Kantor, F A C P , Colonel, (MC), U S Army, discussed "Digestive Symptoms in the Tuberculous and Their Management" at a joint meeting of the University of Colorado School of Medicine and the National Jewish Hospital in Denver, Colo , November 2, 1942

Dr George E Wakerlin, F A C P , Professor and Head of the Department of Physiology of the University of Illinois College of Medicine, Chicago, Ill , is directing research in experimental renal hypertension at the University The John and Mary R Markle Foundation has authorized a grant-in-aid of \$7,000 over a two-year period for the support of this research

The Association of Life Insurance Medical Directors of America held its fifty-third annual meeting in Philadelphia, Pa , October 21-22, 1942 Among the speakers were

- Eugen G Reinartz, F A C P , Colonel, (MC), U S Army—"Effect of Flight on Man",
Dr Frank N Wilson, F A C P , Ann Arbor, Mich—"The Precordial Electrocardiogram",
Dr Edward A Strecker, F A C P , Philadelphia, Pa—"Military Neuropsychiatric Disabilities and Their Treatment"
-

The Los Angeles Heart Association held its twelfth annual symposium on cardiovascular disease in Los Angeles, Calif , November 12-13, 1942 Among the speakers were

- Dr John M Askey, F A C P , Los Angeles, Calif—"The General Practitioner and His Choice of a Digitalis Preparation",
Dr Morris H Nathanson, F A C P , Los Angeles, Calif—"Practical Use of Adrenalin and Related Compounds in Cardiovascular Disease",
Dr Harold J Hovie (Associate), Los Angeles, Calif—"Rupture and Other Complications of Myocardial Infarction"
-

Dr Oscar O Miller, F A C P , Louisville, Ky , was named one of the vice presidents of the Kentucky State Medical Association at its annual meeting in Louisville, October 1, 1942

The Wayne County (Mich) Medical Society, the Detroit District Dental Society, the Detroit Physiological Society, the Detroit Pediatric Society, and the Engineering Society of Detroit have arranged a series of lectures on nutrition in medicine, dentistry, and industry The first lecture in this series was presented on October 12, by Dr Tom D Spies, F A C P , Birmingham, Ala , who spoke on "Recent Advances in Vitamin Research" On November 19, 1942, Dr Anton J Carlson, F A C P , Chicago, Ill , spoke on "What's Wrong with America's Diet?"

Dr S Bernard Wortis, F A C P , Associate Professor of Neurology at the New York University College of Medicine, has been appointed the first Lucius N Littauer Professor of Psychiatry and Visiting Neuropsychiatrist in charge of the psychiatric division of Bellevue Hospital. The appointment of Dr Wortis became effective October 1, 1942. This professorship has been named in honor of the philanthropist who last year established a fund of nearly \$250,000 for "research in psychiatry, neurology and related fields, in order to increase and diffuse knowledge of the biological and other factors which influence thought and conduct, and thereby to prevent and correct abnormal human behavior through clinical and experimental approaches."

The Oklahoma City Clinical Society held its twelfth annual fall conference October 26-29, 1942. Dr James E Paullin, F A C P , President of the College and President-Elect of the American Medical Association, was the guest of honor. Among the guest speakers at the conference were Dr Sara M Jordan, F A C P , Boston, Mass , Dr Byrl R Kirklin, F A C P , Rochester, Minn , Dr Tom D Spies, F A C P , Birmingham, Ala , and Dr Willard O Thompson, F A C P , Chicago, Ill.

Dr Albert E Russell, F A C P , U S Public Health Service, New York, N Y., spoke on "Problems of Civilian Medical Service in War Times" at a meeting of the Cambria County Medical Society at Johnstown, Pa , October 8, 1942.

Dr Walter M Boothby, F A C P , Rochester, Minn , spoke on "Recent Research in the Mayo Aero Medical Unit" and Eugen G Reinartz, F A C P , Colonel, (MC), U S Army, spoke on "Neuropsychiatric Aspects of Aviation Medicine" at the annual meeting of the Aero Medical Association of the United States in Indianapolis, Ind , September 3-5, 1942.

The Association of Military Surgeons held its annual meeting at San Antonio, Tex , November 5-7, 1942. Among the speakers were the following:
 James C Magee, F A C P , Major General, (MC), U S Army, The Surgeon General—"An Appraisal of the Medical Department at War",
 Dr Charles M Griffith, F A C P , Washington, D C—"Medical and Hospital Service Experience with Disabled Veterans of World War II",
 Charles R Reynolds, F A C P , Major General, (MC), U S Army, Retired, Harrisburg, Pa—"Medical and Epidemiological Follow-Up of Selective Service Men Rejected for Military Service",
 Leonard G Rowntree, F A C P , Colonel, (MC), U S Army—"Selective Service System—Wartime Problems of Selective Service",
 Dr Neil D Buie, F A C P , Marlin, Tex—"The Work of the State Medical Association of Texas on Procurement and Assignment Service for Doctors, Dentists and Veterinarians."

The Southern Medical Association held its annual meeting in Richmond, Va , November 10-12, 1942. Among the speakers were:
 Henry M Thomas, Jr , F A C P , Lieutenant Colonel, (MC), U S Army—"Peptic Ulcer in the Army",
 Dr Robert Wilson, Jr , F A C P , Charleston, S C—"Acute Hemolytic Anemia in Fertilizer Workers: A New Industrial Hazard",

- Dr William Henry Sebrell, Jr, F A C P, U S Public Health Service, Bethesda, Md —“Foods and Their Importance to the War Effort”,
- Dr Francis M Rackemann, F A C P, Boston, Mass —“The Natural History of Asthma”,
- Dr Robert L McMillan (Associate), Winston-Salem, N C —“Ventricular Tachycardia as a Therapeutic Problem in Coronary Thrombosis”,
- Leon H Warren (Associate), Major, (MC), U S Army —“Patch Tests Their Practical Applications and Limitations ”

On November 11, 1942, Dr James E Paullin, F A C P, Atlanta, Ga, President of the American College of Physicians, was the guest speaker at a wartime luncheon sponsored by the Southern Medical Association for the officers of the Association, presidents, presidents-elect, secretaries and editors of state medical associations in the South. Dr Paullin spoke on “The Value of Medical Organizations in the War Effort ”

Dr Parley Nelson (Associate), Rexburg, has been named President-Elect of the Idaho State Medical Association

Dr Italo F Volini, F A C P, Chicago, Ill, spoke on “The Oral, Intravenous and Intra-Abdominal Uses of Sulfonamides” at a postgraduate conference, October 22, 1942, sponsored by the Illinois State Medical Society in cooperation with the Peoria County Medical Society in Peoria, Ill

On December 10, 1942, Edgar Erskine Hume, F A C P, Colonel, (MC), U S Army, spoke on “War and Medicine” at a lecture for the public sponsored by the New York Academy of Medicine

Dr Tom Lowry, F A C P, Professor of Clinical Medicine, has been appointed Dean of the University of Oklahoma School of Medicine, Oklahoma City. Dr Lowry succeeds Dr Robert U Patterson, F A C P, who has been Dean since 1935 and is retiring because of age. Dr Lowry will serve from November 15, 1942, to July 1, 1943

Among the speakers at the annual meeting of the Central Society for Clinical Research, held in Chicago, November 6-7, 1942, were

- Dr Raphael Isaacs, F A C P, Chicago, Ill —“Effect of Pectin on the Coagulation of Blood in Thrombocytopenic Conditions”,
- Dr Edgar A Hines, Jr, F A C P, Rochester, Minn —“Experiences with Treatment of Migraine with Potassium Thiocyanate”,
- Dr Clifford J Barborka, F A C P, and Dr Andrew C Ivy, F A C P, Chicago, Ill —“Influence of a Diet Deficient in the Vitamin B Complex on the Work Output of Trained Subjects. Experimental Procedure”,
- Dr Frederick Steigmann (Associate), Chicago, Ill —“Causes of the Drop of the Plasma Vitamin A Level in Liver Diseases ”
-

Dr Francis G Blake, F A C P, New Haven, Conn spoke on “Epidemic Disease in the United States Army ” at a joint scientific meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia, November 11, 1942

The following Fellows of the American College of Physicians are Diplomates of the American Board of Psychiatry and Neurology though they are not so listed in our 1941 Directory

Dr Larue Depew Carter, Indianapolis, Ind
 Dr Andrew C Gillis, Baltimore, Md
 Dr Mark Alexander Griffin, Asheville, N C
 Dr William Ray Griffin, Asheville, N C
 Dr Samuel Bernard Hadden, Philadelphia, Pa
 Arthur Orr Hecker, Major, (MC), U S Army
 Dr Cullen Ward Irish, Los Angeles, Calif
 Dr Henry Ashley Luce, Detroit, Mich
 Dr Andrew Ignatius Rosenberger, Milwaukee, Wis
 James Newton Williams, Lieutenant Commander, (MC), U S Navy

Mellon Institute, Pittsburgh, Pa , is distributing gratis to all interested specialists who request them copies of a publication entitled, "Structure and Antipneumococcic Activity in the Cinchona Series "

DR JAMES D BRUCE NOW VICE-PRESIDENT EMERITUS OF THE UNIVERSITY OF MICHIGAN

Dr James D Bruce, F A C P , former President of the American College of Physicians, retired October 17, 1942, as Vice-President in Charge of University Relations of the University of Michigan, with the title of "Vice-President Emeritus " Dr Bruce has been director of postgraduate medicine at the University since 1928, and vice-president since 1931 He graduated from the Detroit College of Medicine in 1896 and first joined the faculty of the University of Michigan as assistant in internal medicine in 1904 In the succeeding years he served as director of internal medicine at the medical school, chief of medical service at the Hospital, chairman of the division of health service and chairman of the division of health service and chairman of the division of extramural service His organization and direction of post-graduate medical education throughout the State of Michigan is a monument to his leadership and administrative capacity

SPECIALTIES AND SUB-SPECIALTIES AMONG MEMBERS OF THE AMERICAN COLLEGE OF PHYSICIANS

An analysis of the 1941 Directory of the American College of Physicians, and of the 1942 Supplement thereto, presents the following figures These specialties and sub-specialties have been designated by the members themselves It may be reasonable to state that a great many do general internal medicine, though they are primarily interested in certain specific sub-specialties In the classification, Cardiology might reasonably be added to Diseases of the Chest, for undoubtedly this latter specialty does not indicate tuberculosis alone, but the whole range of diseases of the chest, whereas certain members have used the designation "Cardiology" to differentiate from diseases of the lungs

Over the years it is apparent that a very few members have drifted away from Internal Medicine to engage in surgical specialties, the number being 12 primary and 21 secondary

	Primary	Secondary
INTERNAL MEDICINE	3360	88
Allergy	10	156
Arthritis	5	72
Aviation and Military Medicine	11	30
Cardiology	57	714
Diseases of the Chest	117	347
Endocrinology	5	69
Gastro-enterology	43	317
Hematology and Blood Diseases	2	33
Immunology and Preventive Medicine	4	22
Medical Education and Administration	21	36
Metabolic Diseases	11	180
Physical Therapy	—	28
Research	2	47
Tropical Medicine	9	26
Total, sub-specialties	297	2077
TOTAL, INTERNAL MEDICINE	3657	2165
GENERAL MEDICINE	258	18
NEUROLOGY, PSYCHIATRY	217	197
PATHOLOGY, CLINICAL PATHOLOGY	187	132
PEDIATRICS	146	39
RADIOLOGY, ROENTGENOLOGY	102	29
PUBLIC HEALTH, STUDENT HEALTH	62	30
DERMATOLOGY, SYPHILOLOGY	48	51
INDUSTRIAL MEDICINE	16	14
BACTERIOLOGY	12	21
SURGICAL SPECIALTIES	12	12
MISCELLANEOUS		
Anatomy	2	4
Biological Chemistry	2	3
Cancer	1	—
Chemotherapy	—	1
Histology	—	1
Legal-cultural Medicine	1	1
Leprosy	—	1
Life Insurance Medicine	2	3
Medical History	—	1
Nephritis	—	1
Nutrition	—	5
Pharmacology	6	3
Physiology	9	1
Retired	80	—
Toxicology	—	3
Vital Statistics	—	1
Total, Miscellaneous	103	29
NO SECONDARY SPECIALTY GIVEN		2083
	4820	4820

SPECIAL NOTICES

A COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at Michael Reese Hospital by Dr Louis N Katz, Director of Cardiovascular Research. The class will meet each week starting Wednesday, February 17, 1943 for 12 weeks from 7 00 to 9 00

Further information and a copy of the program may be obtained on application to the Cardiovascular Department, Michael Reese Hospital

PRIZE ANNOUNCEMENT

A prize of \$100 is offered by the Menninger Foundation for Psychiatric Education and Research for the best suggestion for a window display in a New York bank presenting the uses and purposes of psychiatry. The window is thirteen feet long, six feet high, and its deepest point about eight feet, it curves so that it is narrower at the ends. It will be seen chiefly by laymen and hence the display should be in the nature of an educational theme, convincingly and graphically presented. It should dramatize the way in which psychiatry can be or is being useful either in the present war emergency or in peace time.

The judges will be Dr George Stevenson, Director of the National Committee for Mental Hygiene, Mr Albert Lasker, of Lord and Thomas, and Dr Lawrence Kubie.

Ideas should be submitted in detail, preferably with drawings or diagrams, directly to Dr William C Menninger, Director of The Menninger Foundation, Topeka, on or before January 31, 1943.

OBITUARIES

DR MAURICE LEWISON

Dr Maurice Lewison, F A C P , died in Chicago of a tumor of the brain on June 17, 1942, at the age of 56. He was born in Worcester, Massachusetts, May 18, 1886, and moved with his family to Chicago when he was 14. Two years later he graduated from Medill High School. In 1906 he received his M D degree from Northwestern University Medical School.

He served his internship in Cook County Hospital and in 1920 took post-graduate work in London. Upon completion of his internship he joined the medical faculty of the University of Illinois and taught physical diagnosis and tuberculosis almost to his death. He was a full Professor in the Department of Medicine. He took his work seriously and was most meticulous in attendance. He was a lucid and forceful teacher. He always stressed the important and continually emphasized the value of bedside observation.

Dr Lewison early became interested in tuberculosis, both from the medical and social aspect. After a long apprenticeship in the dispensaries of the Municipal Tuberculosis Sanitarium he became attending physician in the department of tuberculosis of Cook County Hospital. He was soon appointed Chief of Service and was Consultant at the time of his death.

In 1919 he was appointed attending physician in medicine in Mount Sinai Hospital. Within the walls of this institution Dr Lewison did his best work and spent the happiest years of his life. His ability, sincerity of purpose, and common sense soon won for him the appreciation of Staff and the Board. He became President of the Medical Staff and at the expiration of his tenth year in office was unanimously elected Honorary President. Until his very death he maintained a deep interest in the hospital and its growth.

Dr Lewison was a member of the Chicago Medical Society, Illinois Medical Society and the American Medical Association. He held memberships in the Chicago Tuberculosis Society, Chicago Heart Association, the Institute of Medicine and was certified by the American Board of Internal Medicine. He became a Life Member of the American College of Physicians in 1941. He was an able clinician whose counsel was sought frequently by younger colleagues not alone because of his wide experience in medicine, but also his good common sense and warm friendliness. He was senior author of a Manual of Physical Diagnosis.

Dr Lewison was a member of the Phi Delta Epsilon Medical Fraternity. As a teacher and physician he was deeply interested in the development of the Medical Department of the Hebrew University of Palestine and gave without stint of his time and substance to its cause.

He had a keen civic sense and every appeal for the common weal found in him warm response and whole hearted support. He served on the boards of many charitable institutions of the city.

In his death Chicago sustained a deep loss—the city a good citizen, the medical profession a fine physician, and his many patients a capable healer of a kindly and understanding heart. Mount Sinai Hospital lost a very devoted friend of unusual organizing ability, fine judgment, and deep loyalties.

He is survived by his wife, his son, Edward F. Lewison, a graduate of the University of Chicago and Johns Hopkins Medical School, now on active duty as Captain in the Medical Corps of the United States Army, and a daughter, Ethel Mae, a senior at the University of Chicago.

ISADORE M. TRACE, M.D., F.A.C.P.

DR. H. RAWLE GEYELIN

Dr. H. Rawle Geyelin, F.A.C.P., New York, N.Y., was born in Villanova, Pa., on May 12, 1884, and died on September 7, 1942. He received his A.B. degree from the University of Pennsylvania in 1906 and his M.D. degree from the University of Pennsylvania School of Medicine in 1909. From 1913 to 1916 Dr. Geyelin was Instructor in Clinical Pathology at Columbia University College of Physicians and Surgeons, from 1916 to 1917, an Associate in Clinical Pathology, from 1917 to 1921, an Associate in Medicine, and since 1921, an Assistant Professor of Medicine at this University. From 1912 to 1916 he was Blumenthal Fellow in Medicine at Presbyterian Hospital, from 1915 to 1921, an Assistant Visiting Physician, from 1918 to 1919, Chief of the Medical Clinic of the Vanderbilt Clinic of this Hospital, and since 1921, Associate Attending Physician. Dr. Geyelin served as Consulting Physician from 1923 to 1928, Assistant Visiting Physician from 1928 to 1932 and since 1932 as Associate Attending Physician at Babies Hospital. Since 1929 he was a member of the Medical Board of Doctors Hospital.

Dr. Geyelin was a member of the New York Academy of Medicine, the New York Clinical Society, the Interurban Clinical Club, the Harvey Society, the Medical Society of the State of New York, the American Association for the Advancement of Science, the American Clinical and Climatological Association, the American Institute of Nutrition, the American Society for Clinical Investigation, the Association of American Physicians, and the Society for Experimental Biology and Chemistry. He was a Diplomat of the American Board of International Medicine, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1937.

Dr. Geyelin was the author of many articles which were published in outstanding medical journals.

Dr. Geyelin was one of the outstanding internists and his death is a great loss to the medical profession and to the teaching staff of the College of Physicians and Surgeons.

ASA L. LINCOLN, M.D., F.A.C.P.

Governor for Eastern New York

DR WILLIAM JOSEPH RYAN

Dr William Joseph Ryan, F A C P, Pomona, N Y, was born on December 22, 1889, in Norway, Herkimer County, New York, and died on February 20, 1942. He received his medical degree from the Albany Medical College in 1915 and served his internships and houseship in the Homeopathic Hospital of Albany, the Faxon Hospital of Utica and Metropolitan Hospital of New York City. He was resident physician at the Otisville Municipal Sanatorium for two years, following this appointment he was Director of the Tuberculosis Division of the United States Veterans Bureau in 1920. In 1921 he became Superintendent and Medical Director of the Summit Park Sanatorium. In addition to this he was Director of the Rockland County Chest Clinic, Consultant in Diseases of the Chest at the Nyack, Good Samaritan (Suffern), Rockland State (Orangeburg) and Tuxedo Memorial (Tuxedo Park) Hospitals, and Letchworth Village (Thiells). He was former President of the New York State Association of Superintendents and Boards of Managers of County Tuberculosis Sanatoria, former Chairman, Tuberculosis Sanatorium Conference of Metropolitan New York, Secretary of the Rockland County Medical Society, Vice President of the Eastern Section of the American Trudeau Society, member of the New York Society for Thoracic Surgery, New York State Medical Society, American Medical Association, American Sanatorium Association, National Tuberculosis Association, International Union Against Tuberculosis, American Association of School Physicians and American Public Health Association, Fellow of the American College of Chest Physicians, Fellow of the American College of Physicians since 1937. He served during World War I with the rank of First Lieutenant. He was the author of many published articles.

Dr Ryan made a very enviable record in the various posts which he held and was one of the outstanding chest men of this state. His untimely death was a real loss to the medical profession.

ASA L. LINCOLN, M D, F A C P.

Governor for Eastern New York

DR LEON EARL KING

Dr Leon Earl King (Associate) of Hot Springs, Arkansas died July 10, 1942. Dr King was born in Russia May 23, 1908, and came to this country in his early teens. He was graduated from the High School of Little Rock, Arkansas, with the highest honors and after receiving his Bachelor of Science degree in medicine from the University of Arkansas in 1929, received the Doctor of Medicine degree from the University of Arkansas in 1931. He served internships at Jewish Hospital in St. Louis, Missouri, and the Leo N. Levi Hospital in Hot Springs, Arkansas.

Dr King practiced for ten years in Hot Springs, where he was a member in good standing of the Garland County Medical Society, the Arkansas Medi-

cal Society, the American Medical Association and the American College of Physical Therapy. He became an Associate of the American College of Physicians in 1938. He was on the staff of the Leo N. Levi Hospital and St. Joseph's Hospital.

Although he lived sixty miles away, Dr. King took time to instruct some of the students at the University of Arkansas Medical School.

In many ways Dr. King was an unusual person. He was a student of languages, particularly French, Russian, German and Latin, and in spite of his foreign birth and early training he had mastered the American language so that he could speak without accent.

Professionally he was particularly interested in arthritis and had published several articles on this disease, the last one appearing in the April, 1942 issue of the *Arkansas Medical Journal*. He was held in high esteem by all his confreres in Hot Springs and his untimely death by a skull trauma has removed one of the ablest practitioners from the profession.

OLIVER C. MELSON, M.D., F.A.C.P.,
Governor for Arkansas

DR. RAYMOND A. RAMSEY

Dr. Raymond A. Ramsey, of Columbus, Ohio, died August 19, 1942. He was born in 1886 and received his medical degree at Western Reserve University School of Medicine in 1912. He became Instructor in Medicine at Ohio State University College of Medicine and was later Visiting Physician at White Cross, Mount Carmel and Grant Hospitals.

In 1931 he became Senior Attending Physician at Grant Hospital and in 1932, Senior Attending Physician at Mount Carmel Hospital. In 1933 he became Consulting Physician at Children's Hospital and in 1934 was appointed Endocrinologist of the Student Health Service of Ohio State University.

He became an Associate of the College in 1924 by virtue of his membership in the American Congress on Internal Medicine. He was a member of the Columbus Academy of Medicine, the Ohio State Medical Association and the American Medical Association.

Dr. Ramsey was an earnest student and occupied an enviable position as an internist in the State of Ohio. His many grateful patients, as well as his brother practitioners, mourn his passing so early in such a useful life.

A. B. BROWER, M.D., F.A.C.P.,
Governor for Ohio

DR. WARREN C. BREIDENBACH

Dr. Warren C. Breidenbach, F.A.C.P., of Dayton, Ohio, died June 29, 1942. He was born in Piqua, Ohio, on January 27, 1894, a son of Conrad W. and Elizabeth C. Steller Breidenbach.

Dr Breidenbach received his preliminary education in Piqua and Dayton, and attended the University of Michigan, receiving his B A degree in 1914. He was graduated from the University of Michigan Medical School in 1917.

He was an interne and later resident physician at the Miami Valley Hospital. He entered the general practice of medicine and gradually developed his specialty in tuberculosis. He became Superintendent of the Stillwater Tuberculosis Sanatorium in 1919. He was also a member of the staff of Miami Valley Hospital, Good Samaritan Hospital, and a consultant at the Ohio Soldiers' and Sailors' Home at Xenia.

Dr Breidenbach was a member of the Montgomery County and Ohio State Medical Societies, of the Mississippi Valley Tuberculosis Conference, and a Fellow of the American Medical Association. He was also a Fellow of the American College of Physicians, a member of the Trudeau Society, a member of the American College of Chest Physicians, a Diplomate of the American Board of Internal Medicine, and an assistant Fellow of the College of Thoracic Surgery.

He was especially interested in planography and developed it successfully in his study of tuberculosis. He is survived by his wife, Mrs Elaine R Breidenbach, two sons, Warren C, Jr, and Frederick, and a daughter, Jane. Dr Breidenbach was highly successful in his specialty of tuberculosis. He devoted much of his time to a study of the prevention and treatment of tuberculosis in the indigent and many of his patients, especially from this group, will mourn his passing.

A B BROWER, M D, F A C P,
Governor for Ohio

DR FRANCIS BACON CAMP

Dr Francis Bacon Camp, F A C P, died in St John's Hospital, Springfield, Mo, on August 11, 1942. This brought to a close a life crowded with hard work and a considerable measure of success. Dr Camp was widely known as an internist, and was also prominent in the social life of Springfield.

Born on December 31, 1896, in the city in which he died, he received his collegiate education at Westminster College and his medical education at Emory University. He served his internship in the St Louis City Hospital, and after two years of further training began his practice in Springfield in 1925. He soon rose to prominence locally and throughout southwestern Missouri. He was deeply interested in developing the library of St John's Hospital, and his friends are creating a memorial fund in his honor to be used to develop the library.

He was elected a Fellow of the American College of Physicians in 1941, and certified as an Internist by the American Board of Internal Medicine in 1939.

Hard work, devotion to his patients in a personal way, no doubt con-

tributed to the development of heart disease which eventually closed his career. He is survived by his widow, Mrs. Mary Peake Camp, a son, Walter Camp, and a daughter, Sally Camp, a brother, Dr. George Camp, and a sister, Mrs. Louis Spalding.

To these, we join his many friends and old patients in extending sympathy.

RALPH A. KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

DR. WILLIAM FORSYTH MILROY

Dr. William Forsyth Milroy, a Fellow of the College since 1920, died at his home in Los Angeles, California, after a brief illness, at the advanced age of 87.

Dr. Milroy was born December 28, 1855, at York, New York. He received his premedical training at the University of Rochester. Following this he spent one year at Johns Hopkins University, one year at the College of Physicians and Surgeons at Baltimore, and was awarded his medical degree at Columbia University College of Physicians and Surgeons in 1883. He served his internship at the New York City Hospital and the New York Maternity Hospital.

For many years he practised medicine at Omaha, Nebraska, where he was an indefatigable worker, becoming successively President of the Omaha-Douglas County Medical Society, the Nebraska State Medical Association, and the Medical Society of the Missouri Valley. He was also Vice-President of the American Therapeutic Society in 1923. For 49 years he was Professor of Clinical Medicine at the University of Nebraska College of Medicine, in which capacity he was a source of the highest inspiration to the men with whom he came in contact.

Dr. Milroy made several contributions to the annals of medical lore, one of which, entitled "An Undescribed Variety of Hereditary Oedema," earned for him the distinction of being the discoverer of a pathologic condition henceforth to be known among medical men as "Milroy's Disease."

ROY E. THOMAS, M.D., F.A.C.P.,
Governor for Southern California

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